MYASTHENIA GRAVIS.

By Charles S. Myers, M.A., M.D.

Reprinted from The Journal of Pathology and Bacteriology. *Edinburgh and London*, Young J. Pentland, *September* 1902.

MYASTHENIA GRAVIS.

MYASTHENIA GRAVIS.[1]

By Charles S. Myers, M.A., M.D.

PART I.

On the History of the Recognition, the General Character, and the Differential Diagnosis of the Disease.

My attention was first drawn to this disease by the following case, which came under my care while I was house physician at St. Bartholomew's Hospital to Dr. S. Gee, who has kindly permitted me to publish it here. Unfortunately, Dr. Gee was away from London whilst the case was in his wards.

Case 1.—Elizabeth D., æt. 22, a confectionery-packer, was admitted on August 10, 1899, to Hope Ward, suffering from dysphagia. Her family and personal history of disease was unexceptional. She had never had diphtheria, nor had she before suffered from her present symptoms. At Christmas 1898 her eyes became weak. Objects seemed to "run into one another." For this she saw an optician and began to wear glasses, but with little or no benefit. At dinner on Good Friday 1899 she suddenly noticed that she could not swallow her food; in the evening of that day she choked at supper, liquid returning through her nose. Since then she has had occasional difficulty in swallowing. In June 1899 she first began to have difficulty in closing the jaws. About the same time she noticed that her speech was becoming indistinct. Occasionally she had loss of power in the arms, particularly in the extensor muscles. Sometimes she had pain at the back of the head. In July 1899 she noticed commencing weakness of the muscles of the eyelids and eyeballs. First the left lid drooped and could not be raised. Later this recovered itself, and the right lid fell; at the same time the patient noticed that her left eye when uplifted turned outwards. She could not now go out alone, as she could not see the street traffic on either side of her. For two weeks before admission she had been attending the out-patient department of the hospital, where a provisional diagnosis of hysteria had been made.

Condition on Admission.—A delicate, dark, fairly nourished, nervous-looking girl. Her mouth was open, this giving a vacant expression to her face. She had incomplete double ptosis, and could neither lift the lids fully nor close them tightly. On the right side, movements of the eye were limited markedly and equally in all directions, in the left eye more especially in an outward and downward direction. When she looked up, the left eye almost disappeared beneath the eyelid. She had an upward squint of the left eye.

[1] A thesis for the degree of M.D. at Cambridge in 1901. Save that it has been condensed, and for a few suggestions, which I owe to Professor Clifford Allbutt, and for the addition of one or two recent cases, the essay has not been materially altered.

By covering one eye, the movements of the other were improved. There was frequent lachrymation. The pupils were equal and reacted normally. The fundi were natural. There was no hemianopsia. The muscles of the face reacted well electrically, and the movements of the expression were good. While eating, her lower jaw dropped, and she had to support it with her hand. The lips, on the other hand, met easily. With effort, after persuasion, she could close her teeth. The tongue was protruded naturally. There was no nasal obstruction. The palate moved feebly but symmetrically. The speech was thick and indistinct, often resembling that of a person with cleft-palate in whom part of the expired air escapes by the nose. The chest and abdomen were natural. She could walk well with normal gait. Nothing unusual was noticed in the limbs. Sensation was normal. Knee jerks feeble. The palatal reflex was present but very weak. The urine was free from albumin and sugar. All the muscles reacted well to fairly strong faradic currents. Indeed faradism seemed to improve subsequent volitional contractions. She could usually close her jaw with fair force during and after the application of the faradic current. She was much afraid of the electrical treatment, crying out even if no current was passed through the applied electrodes.

On August 16 a note was made to the effect that treatment with strychnine and the faradic current seemed to be improving the patient's condition, and that the extent of ocular paresis varied from day to day.

On August 20 I noted that she still used her hands to raise the lower jaw, and I determined to try the effect of putting her hands into splints, and of having her spoon-fed by a nurse. Accordingly at 1.15 P.M. the nurse began to give her a little fish and milk. The girl swallowed one or two mouthfuls, but complained that she could swallow no more. She took some milk, and then said, "I am choking." She stopped breathing and became blue. When I came into the ward, the Sister was employing artificial respiration and oxygen inhalations, and had thereby much reduced the patient's cyanosis. I could feel no food in the throat. I gave a hypodermic injection of 3 minims of the hydrochloride solution of strychnine, and stayed the artificial respirations, allowing the patient to take a series of voluntary respirations. These were shallow, the sterno-mastoid and accessory muscles of respiration being the chief agencies. The pulse was of fair volume and distinctly felt at the wrist. She was again becoming cyanosed. The tongue was pulled out, and artificial respiration was once more resorted to. Air entered both lungs freely. The conjunctivæ remained sensitive. Once or twice the patient resisted these respiratory movements, raising her hand to her jaw as if she thought she could breathe better in that way. Some crepitations were now noticed at the apex of the right lung. For one minute the faradic current was applied to stimulate the intercostal and phrenic muscles of the patient. Then for a third time artificial respiration became necessary. But by this time the pulse was feebler and the air entry poor; indeed, into the right lung no air appeared to enter. Five more minims of strychnine were injected hypodermically. The intercostal muscles and the diaphragm no longer moved during her few respiratory efforts. She again became intensely cyanosed. Finally, finding artificial respiration of no avail, I performed a desperate, hurried tracheotomy, but no air subsequently entered the chest. The heart stopping at 1.35 P.M., the patient died without a struggle or recession of the chest even to the end.

NECROPSY.—On the following day Dr. Morley Fletcher performed the post-mortem examination. Save for the cicatrix of an old gastric ulcer, a small and fatty heart with atheromatous patches on the aorta near the valves, nothing macroscopically abnormal was found. The brain weighed 40 oz. Except in the lowest part of the bulb, which was unfortunately hardened in Müller's fluid, a general examination of the cerebro-spinal nuclei was made by Nissl's method of staining, in addition, of course, to the usual Weigert-Pal and Marchi

methods. Drs. F. E. Batten and H. Morley Fletcher have already published (2) the results of these microscopical examinations, together with a brief clinical abstract of the case. The following is a concise summary of their report:—

The cells of the third, the seventh, and the ninth cranial nuclei were unusually swollen, the granules of Nissl no longer retained their triangular form, but were fragmentary, smaller than usual, and irregularly or diffusely distributed throughout the cell substance. The nuclei of the cells stained and were placed naturally; those of the cells of the third nucleus were somewhat small. The cells of the fifth and sixth nuclei were normal, they were well stained, and their dendritic processes were good. The cells of the anterior horn in the cervical, dorsal, and lumbar regions of the spinal cord were normal, save that the chromatophilic substance was occasionally replaced by a yellowish-brown pigment,[1] which in osmic acid preparations was stained brown and had a granular appearance.

The cerebral cortex, the peripheral nerves, and the muscles were not microscopically examined.

After the above description I need not remark that I was wholly unprepared for the sad issue of this patient's illness. I assumed that the case was an unusual example of hysteria. Not until after the necropsy was my attention called to a recognised group of similar cases, often fatal owing apparently to bulbar failure, in which, after death, no accountable lesion was discoverable. Only three such cases had then been published in England, namely, by Wilks (3), Shaw (4), and Dreschfeld (5). Abroad, more particularly in Germany, a greater number had been described. I have gathered together in an appendix condensed accounts of all the undoubted cases of this disease I can find in which a post-mortem examination has been made.

The history of the gradual recognition of the disease from a study of such cases may be thus summarised.

In 1877 Wilks (3) described what is generally accepted as the first recorded case terminating in fatal, apparently bulbar, paralysis, in which no lesion was discoverable by macroscopical and microscopical examination of the bulb. This was followed by the publication of three cases with similar symptoms by Erb (6) in the next year, only one of which, however, proved fatal; no examination post-mortem was made. Ten years later the negative results of an autopsy on another similar case were published by Oppenheim (7). Still later, Shaw (4) in 1890, Jolly (8) in 1891, Dreschfeld (5) in 1893, Strümpell (9) in 1896, Hall (10) in 1899, and Goldflam (22a) in 1902, recorded fatal cases, in which careful examination of the central nervous and often of the peripheral nervous and muscular systems revealed no lesions whatever. In 1887 a case examined by Eisenlohr (11) showed recent minute hæmorrhages and hyperæmia in the region of the sixth nucleus. Nuclear hæmorrhages, all recent, were likewise found by Hoppe (12) in 1892, by Toby Cohn (13) in 1893–97, by Charcot and Marinesco (14) in 1895, by Schüle (15) in 1899, and by Oppenheim (20) in 1901, in their published cases of this disease. Moreover, while Strümpell, the first among these writers to use Nissl's mode of staining nerve cells with methylene blue, Toby Cohn, and Goldflam found no changes even by this delicate method, other observers (*e.g.* Batten and Fletcher in my own case, Batten also in an unpublished case, Burr and McCarthy, and Guthrie in 1901) have found

[1] The deposit of yellow pigment appears at the expense of Nissl's granules. It has been variously held to be an expression of functional activity, of senility, or of degeneration change.

slight but definite changes in the chromatophilic substance of certain nuclear nerve cells. In addition to such chromatolysis, a fatal case, observed by Widal and Marinesco ([16]) in 1897, revealed degenerated fibres in certain of the affected cranial nerves, and dilated blood vessels in the central nervous system. Kalischer ([17]) in the same year published an extremely doubtful example of this disease, in which he observed small hæmorrhages, aneurysmal dilatations, and frequent thickening in the walls of the blood vessels of the central nervous system, and degenerative changes throughout the grey matter from the third cranial nucleus downwards. Mayer ([18]), in an evident case recorded in 1894, observed vacuolation in a few cells of the hypoglossal nucleus, and distinct degeneration of the myelin sheath in the intramedullary portions of the hypoglossal and anterior spinal nerve roots. Sossedorf ([20]) found similar changes in the ninth and tenth cranial nuclei and nerve roots. In 1900, Déjerine and Thomas ([19]) published a case in which the cortex cerebri showed a very marked multiplication of its neuroglia cells, and a corresponding diminution in the size of the bodies and dendrites of its nerve cells. But these changes, associated as they were with scattered degeneration throughout the fibres of the pyramidal system, need only be noted here ere dismissal from further discussion, as they are obviously indicative of a pseudo-bulbar paralysis which differs materially from the disease now under consideration.[1]

So far I have been speaking of the disease as if it were invariably fatal. But although I intend to confine my remarks mainly to those cases in which a necropsy has been performed with negative (or practically negative) results, I ought to insist at once that, as our knowledge of the disease has increased, numerous cases have been published in which the patient appears to have quite recovered. Campbell and Bramwell ([1]), who have issued the most exhaustive monograph on the subject which has yet appeared,[2] enumerate thirty-four non-fatal cases. To some of these they themselves are inclined to refuse admission; and of several others I am somewhat sceptical. At least three of their cases have since terminated fatally; and in one other there has been a second attack. Now since this new disease is distinguished by the surprisingly negative results generally yielded by it after death, *we shall clearly be treading on surer ground if we confine ourselves in the main to a study of the symptoms exhibited by completely recorded fatal cases*, rather than if we admit into our consideration the many doubtful cases which have undergone no autopsy or have ended in recovery.

The description of the first case by Wilks ([3]) is unfortunately so meagre that a diphtheritic neuritis cannot be altogether excluded. It is here given verbatim.

Case 2.—A stout girl, looking well, came to the hospital on account of general weakness: she could scarcely walk or move about, she spoke slowly,

[1] It is, in this connection, perhaps noteworthy that, in the cases showing the signs of disseminated sclerosis but without corresponding lesions, Strümpell ([19a]) noted a leathery consistence of the greater part of the brain and, in slight degree, a crossed pyramidal degeneration.

[2] After this had been written, Professor H. Oppenheim ([20]) published in 1901 an elaborate work on Myasthenia Gravis, which, however, I did not see until I had almost finished preparing the thesis for the press. I am indebted to him for the notes of three of the cases in the Appendix, but I have been able to collect a greater number of completely examined fatal cases than has yet been published, and I have reported them, I hope, with greater accuracy and in sufficient detail.

and had slight strabismus. The house physician was inclined to regard the case as one of hysteria; as he possessed a special knowledge of eye affections, he saw nothing in the strabismus incompatible with that view. She remained in this state about a month, being neither better nor worse; she was able to walk about, but every movement of her limbs and speech was performed so slowly and deliberately, that the case seemed rather one of lethargy from want of will than an actual paralysis. At the end of this period all the symptoms became aggravated, and in about three days they had assumed all the well-marked characters of bulbar paralysis. She spoke most indistinctly, swallowed with great difficulty, and was quite unable to cough. The limbs were, however, not paralysed as she was able to get out of bed. It was shortly after seen that her respiration was becoming affected, the difficulty of which rapidly increased, and in a few hours she died. The medulla oblongata was very carefully examined, and no disease was found. It appeared quite healthy to the naked eye and the microscope discovered no manifest change in the tissue.

The great name and position of Erb ([6]), who in the following year described three cases under the title *Ein eigenartiger wahrscheinlich bulbärer Symptomen-Komplex*, secured for the disease its recognition as Erb's disease by Murri ([21]) and certain later writers.

Among other names which have been successively given to it are "Chronic progressive bulbar paralysis without discernible lesion" (Oppenheim) ([7]), "Progressive external ophthalmoplegia with final bulbar paralysis" (Eisenlohr) ([11]), "Myasthenia gravis pseudo-paralytica" (Jolly) ([8]), "Association of bulbar symptoms involving also the limbs" (Goldflam) ([22]), "Subacute polio-encephalomyelitis without anatomical lesions" (Dreschfeld) ([5]), "Asthenic bulbar palsy, type of Erb-Goldflam" (Strümpell) ([9]), "Subacute descending superior bulbar paralysis" (Charcot and Marinesco) ([14]), "Asthenic paralysis" (Fajersztajn) ([23]).

A glance at the varying nomenclature of the malady suggests the more prominent of its now recognised signs and symptoms. Perhaps the grave issue of the disease, that is to say, the final implication of movements controlled by bulbar nerves, was the first feature to draw attention to it as a distinct and definite malady. At all events, until Jolly gave it the name of "Myasthenia gravis pseudo-paralytica," little was known of its further characters, and it was described merely as a peculiar variety of progressive bulbar palsy. Some, certainly, had noticed the chronic nature, the varying exacerbations and remissions in the course of the disease, and the implication of the limbs; but Jolly was the first to take graphic records of a patient's muscular contractions, thereby revealing one of the most striking features of the disease. Erb had observed that in one of his cases the muscles of the lower limbs became quickly fatigued by walking; and Oppenheim and Bernhardt had noted that their respective patients could not close their jaws after they had been chewing for a short time. Yet to Jolly ([8]) belongs the credit of first pointing out that this disease, myasthenia gravis, as we shall hereafter call it, is characterised by an abnormal liability of voluntary movements to tire throughout the whole body. His observations were soon confirmed by Goldflam ([22]) in 1893, and by Strümpell ([9]) in 1894.[1]

The myasthenic reaction is thus described by Jolly. If to the motor nerve of a striped muscle a faradic current of constant

[1] Oppenheim ([20]) gives the credit of this discovery to Goldflam, as in 1891 Jolly's case had not been with sufficient certainty identified.

intensity be alternately applied and discontinued for a small but adequate number of times, each period of tetanisation and of rest lasting a few seconds, the tetanus so produced in the muscle will gradually diminish in force and extent, until finally only at the instant of each reapplication of the current a brief contraction occurs,—similar to that produced by the closure of a constant current,—while during the passage of the current the muscle remains in a state of very feeble contraction, or perhaps exhibits no contraction at all. If the intensity of the current be now increased, or if after a pause of thirty seconds or more the original strength of current be reapplied, a repetition of these phenomena will be obtained, namely, a tetanus at first persisting throughout the application of the stimulus, followed by others of gradually diminishing intensity, and finally ending in exhaustion. Also if the faradic current be applied without intermission during a period varying from twenty-five seconds to a minute, a similar diminution in contractile power will be observed, which sooner or later, according to the strength of the stimulus and the stage of the disease, gives place to a condition of complete relaxation. This series of phenomena constitutes Jolly's myasthenic reaction.

It is to be borne in mind that no feature of this disease is so marked as the irregularity of its course. At one moment the patient shows abnormal exhaustibility in one part; in a few days or weeks he may be well, or he may develop the same sign in another part. It is perhaps a result of this irregularity that the myasthenic reaction has not always been discovered in cases which otherwise exemplified the type of the disease. In one case, at least, in that of Wernicke, a subsequent observer, Toby Cohn ([13]), failed to corroborate the previous discovery of abnormally rapid exhaustibility. The muscles of the limbs are the most convenient for the demonstration of the reaction. Possibly in certain fatal cases of myasthenia gravis, where the limbs were not obviously affected, and the myasthenic reaction was unobserved, the characteristic electric action would with care have been elicited from the muscles of deglutition or respiration.

The myasthenic reaction clearly demonstrates an extraordinary inaptitude for prolonged muscular activity. The same condition is reflected in the volitional muscular actions of such patients. The typical condition of the voluntary muscles in cases of myasthenia gravis is that, at the beginning of the day or after adequate rest, they react normally or fairly well; but towards evening or after use, they become tired out and contract feebly, if at all.

We have thus before us three signs which may be described as pathognomonic of myasthenia gravis. They are—(1) ready fatigue of certain or general voluntary movements either to a succession of tetanising currents applied to the nerve or to volitional impulses descending from the brain; (2) the exacerbations and remissions shown in the course of the disease; and (3) the tendency to a fatal

implication of the muscles innervated by the bulb. To these must be added other very important general signs, mainly of a negative character:—(4) There is no reaction of degeneration; the muscles react to a faradic current of normal intensity, or more often require one somewhat stronger. (5) The muscles, as a rule, show neither atrophy nor fibrillar contraction. (6) Sensation and intelligence are unimpaired. (7) The reflexes may be normal, are often feeble, but perhaps most frequently are somewhat exaggerated. Clonus is absent. (8) Purely voluntary muscles are alone affected.[1] The mechanisms of defæcation and micturition are never impaired. (9) The myasthenia, although often unequally marked on the two sides, is almost invariably bilateral.

From these general features of myasthenia gravis we may proceed to note the characters which mark it off from other more or less similar diseases.

It is of vital importance to distinguish myasthenia gravis from hysteria, that limbo to which physicians are prone to relegate all neuro-muscular diseases that present difficulties of diagnosis. For my own part, I confess, I imagined that my case was one of hysteria, because I knew of no disease with those of which its features would coincide. In the case observed by Clifford Allbutt ([24]), the significance of the symptoms was likewise not fully understood. Indeed, myasthenia gravis has been many times diagnosed and treated as hysteria. I have described the diagnosis of this disease from hysteria as one of vital importance, because muscular exercise, faradic stimulation, and scolding, however gentle, are above all to be avoided in cases of myasthenia gravis. None of the stigmata of hysteria has been found in this disease. Disturbances of sensation are almost invariably absent. The difficulties of swallowing and breathing are such as arise from obvious weariness, not from spasm or from lack of co-ordination; the disorders of speech arise from palatal, lingual, and labial paresis. In hysteria the voice is never nasal, but the vocal cords are inactive—a condition but seldom met with in the last stage of myasthenia gravis. In hysteria, external ophthalmoplegia and implication of the orbicularis oculi and levator palpebræ superioris muscles are rare, if not unheard of, conditions: they are among the most common affections in myasthenia gravis.

From chronic bulbar paralysis, the extraordinary remission and exacerbation of symptoms, the frequent implication of the higher nuclei and of those innervating the trunk and limbs, the general absence of muscular atrophy, of fibrillar contractions, and of degenerative electrical variations are among the most prominent points of distinction.

To prevent confusion between myasthenia gravis and the Landouzy-Déjerine form of progressive muscular dystrophy, it is sufficient to

[1] See, however, Appendix, Case 21, p. 342.

recall the remittent course, the deficiency of other movements in the former disease, however much the expressionless face and waddling gait may in rare instances recall the signs of the latter.

Neuritis is seldom purely motor. Sensory affections are never well marked in myasthenia gravis. The knee jerks are often exaggerated in myasthenia gravis, never, at least for long, absent: they are diminished or absent in most cases of neuritis, while here the myasthenic reaction is unknown. Diphtheritic neuritis may present closely similar bulbar symptoms. The previous history and a possible presence of the reaction of degeneration should be looked to, and the ciliary muscle should be tested.

Too many distinct diseases are included in Landry's paralysis to permit of a satisfactory summary of the points of difference between it and myasthenia gravis. The extremely rapid course and the frequent sensory disturbances are important features in Landry's paralysis.

Neurasthenia differs from myasthenia gravis in yielding no true myasthenic reaction, and in presenting well-marked sensory symptoms.

The distinction between the forms of periodic palsy, amyotrophic lateral sclerosis, and myasthenia gravis is usually clear.

In the chronic variety of polio-encephalomyelitis, the fibrillar tremors and atrophy of the affected muscles, their changed responses to electrical stimuli, and the condition of the tendon reflexes are sufficient guides to a correct diagnosis. But in the acute form of this disease, in superior and inferior polio-encephalitis, and in certain toxic forms of apparently nuclear inflammations, when both ophthalmoplegia and bulbar symptoms may be present, their diagnosis from myasthenia gravis may present considerable difficulties. Usually the rapidity and mode of onset, the general mental condition, and the subsequent course of the disease indicate its real nature.[1]

The myasthenic reaction is not confined to myasthenia gravis. Benedikt ([25]) found in the hemiplegia of cerebral carcinoma an almost identical condition, called by him "Reaction der Erschöpfbarkeit," and characterised by "a diminishing reaction during faradic stimulation, the reaction at the onset possibly being excessive, normal, or defective." Brenner ([26]) has described it in certain cases of apoplectic paralysis. It has also been observed in cases of muscular hypertrophy, chronic poliomyelitis, and Landry's paralysis. Strümpell ([9]), however, points out that in myasthenia gravis the reaction produced is far more abruptly marked, and that it may be obtained in groups of muscles which at the time are not obviously paretic. The myasthenic reaction appears also to have been noticed in persons who suffer from a curious disease of Japan, called *Kubisagari*.[2] Muira ([27]) found, on stimulating

[1] The subject is discussed at length by Oppenheim ([20]), pp. 145–155.

[2] *Kubisagari* literally means a man who droops his head. It is a disease which is found only in country peasants tending horses and cattle, manifests itself in paroxysmal attacks, and very closely resembles a Swiss malady described by Gerlier ([28]) as "Une Epidémie de

with an induction current the splenius muscle of such a patient at intervals of one second, that after twenty stimulations the contractions became weaker and slower, but that after a minute's rest, powerful contractions were again produced.

Careful systematic work, however, is required before it can be decided how far the myasthenic reaction extends to other diseases besides myasthenia gravis.

PART II.

The Determining Conditions, Course, and Detailed Description of the Disease.[1]

Sex.—Of twenty fatal and completely studied cases, thirteen were females, seven were males. In Campbell and Bramwell's (1) collection of sixty cases (which include several of doubtful nature), the disease was almost equally distributed.

Age.—Of twelve certain female cases, the age in nine varied between 16 and 30. In the tenth case the disease had lasted fifteen years in a woman of 36; the ages of the remaining two women were 34 and 48. Of seven completely studied male cases, in two the age was given as 13 and 15, in one as 25, in the other four between 30 and 40. Campbell and Bramwell's tables give the mean age of male subjects of the disease as 35, of female subjects as 24.

Family history.—As a rule, no neuropathic hereditary influence could be obtained. No case is on record where two members of a family have succumbed to the disease.

Occupation.—Nearly all the patients were hard-working members of the lower and lower-middle classes, and were for the most part engaged in manual work.

Immediate cause.—A history of syphilis or of alcoholic abuse was exceeding rare. Overwork and exposure were common antecedents. Headache, frequently of a migraine type, chill, diarrhœa, and other alimentary disturbances were common at the onset. Among the cases included by Campbell and Bramwell, such factors appear as typhoid fever, influenza and the like. They occur in twelve of Oppenheim's fifty-three supposed cases. In a few cases a new growth seemed to have been a proximate cause (cf. later, pp. 325, 326.)

Onset.—This is usually insidious and slow. The first occurrence of muscular weakness was often attended with cervical or sacral pain, occipital headache, photophobia, or vertigo. The muscles earliest attacked were commonly the levatores palpebrarum superiorum, the muscles of mastication or the muscles of deglutition. But a considerable number of patients noticed first a weakness of the limbs. It has been suggested (but on insufficient evidence) that the disease falls earliest on the muscles most commonly used. Thus a cook developed paresis first in his fingers, a housemaid first in her legs.

Vertige paralysant." The attack is often ushered in by giddiness and diplopia, and lasts about fifteen minutes. During this time the patient may be unable to walk or stand, to use his hands, or to bite. There is often ptosis, weakness of the tongue and lips during the attacks, but the mental and sensory functions of the nervous system are unchanged. Bodily exertion and mental excitement increase the number of attacks per diem. The disease is paroxysmal and never fatal; otherwise its resemblance to myasthenia is extraordinarily close.

[1] Only the fatal cases in which autopsies have been performed are here in the main considered. Consequently certain peculiarities noted in doubtful cases, *e.g.* by Gowers (52), find no mention.

Sensory affections.—These were uncommon and, if present, usually insignificant. They are perhaps attributable in many cases to muscular weariness. Migraine accompanied the disease in four cases. Visual and auditory acuity was reduced in two cases. There may have been hysterical complications in Burr and McCarthy's ([51]) case.

Electrical reactions.—A diminished excitability of certain muscles to the faradic and galvanic currents was observed in four well-established cases of the disease; but accurate galvanometrical experiments are still wanting. One case ([28a]) presented slight reactions of degeneration in a single muscle.

Atrophy.—Save in this case (in which the peripheral nerves and muscles were not examined at the autopsy) no reaction of degeneration has been observed. In Dreschfeld's ([5]) case, which lasted fifteen years, there was atrophy but no reaction of degeneration, and no degeneration noted after death. Of twenty-two fatal cases, completely studied, atrophy was expressly declared absent in the majority. Doubtless most of the few cases of Campbell and Bramwell's list, where atrophy is recorded, were in reality either cases of poliomyelitis or neuritis, or cases where emaciation had been mistaken for degeneration. In Sossedorf's case, however, the necropsy revealed atrophy and degeneration of the lingual muscles, while the hypoglossal nuclei and nerves were unaffected.

Reflexes.—The patellar reflex was usually brisk; it was never absent. Clonus was absent. The arm reflexes were often absent. The plantar reflex was of the flexion type. The remarkable decrease of the knee jerk on repeated elicitation, observed by Strümpell and others, is an exaggeration of what occurs in healthy persons; it was not obtained in all cases.

Eye movements.—Paralysis of the intrinsic muscles of the eyes was not recorded in any of the twenty-two undoubted and completely studied cases of this disease. In two the pupils were of unequal size. In twelve there was partial or complete external ophthalmoplegia. In nine diplopia was observed, often a transient symptom. In fourteen of the twenty-two cases ptosis occurred; it is generally incomplete and is a most variable sign, one week present in one eye, the next week present in the other, in both, or in neither. It may be absent immediately after awakening from sleep, or during unusual emotional excitement.

Jaws.—Paresis or palsy of the muscles of mastication was noticed in eighteen of the twenty-two cases. In the most severe cases, fatigue after biting is complained of. Occasionally early stiffness in, or loss of control over, these muscles has been recorded.

The facial muscles.—Total facial palsy or paresis is uncommon; one or other of the three groups[1] generally escapes. The muscles of the face were affected in fourteen of the twenty-two cases. The most commonly observed defect was that the patient could no longer whistle or blow out a candle. Several of the patients could not tightly close their eyes. Implication of the frontalis was not usually noted; sometimes it contracted in order to compensate for the ptosis. In a few cases the face wore a peculiar mask-like expression; in one the naso-labial folds were exaggerated, in two others they were unequal, in a third they were obliterated. In one case the angles of the mouth were drawn downwards, in another outwards. Lagophthalmos was fairly common, but rarely well marked.

The tongue.—In only nine of the twenty-two cases was paresis or palsy of the tongue noticed. The lingual muscles were less commonly involved than any of the other bulb-innervated muscles; in two of the above cases they were expressly declared intact before death. In Dreschfeld's ([5]) case the tongue had

[1] According to Tooth and Turner ([29]) the third nucleus supplies the frontalis and orbicularis oculi, the twelfth nucleus supplies the orbicularis oris, the palate, and the vocal cords.

a somewhat atrophied look; in three cases it was tremulous; in another it appeared pale and thin; only in Sossedorf's case was muscular degeneration observed at the necropsy.

Muscles of deglutition.—Sooner or later, in all the twenty-two fatal cases, these become affected. Repeated attempts at swallowing have to be made before the bolus of food or the liquid passes into the pharynx. The final picture of the disease, drawn by Strümpell, is indeed pitiful, when the patient lies propped up with hands too weak to aid the weary cervical muscles, the head drooping, and a viscid mixture of saliva and mucus falling from the open mouth.

The soft palate.—In twenty-one of the twenty-two completely studied cases, a nasal voice or regurgitation of food through the nostrils was noted. In the earlier stages the nasal voice was developed only after conversation had been for some time prolonged.

The vocal cords.—Of the twenty-two cases, weakness of the abduction muscles was noted in two; weakness of the adduction muscles in two. In no case was there total paralysis. The voice sometimes became hoarse, or lower in pitch. Speech was slow, in some cases having a nasal twang, in others taking on a snuffing character; yet in others resembling the speech of a patient with tonsillitis. The patient was in some cases unable to cry out.

The muscles of respiration.—Attacks of dyspnœa were noted in eighteen of the twenty-two fatal cases, the patient sometimes falling down cyanosed, cold and helpless. In a few cases the dyspnœa was remedied by drawing forward the tongue, which owing to its fatigue had promoted the condition. Sooner or later fatal asphyxia usually followed.

The heart.—The pulse in Laqueur's ([30]) case became slower after experimental exhaustion of the voluntary muscles. In Mendel's ([31]) case it became intermittent towards evening. The cardiac rhythm was not materially affected in most cases of the disease until dyspnœa supervened.

The limbs.—In all save one of the twenty-two completely studied cases the limbs were affected to some extent. In a few patients the large proximal (*e.g.* the deltoid and ilio-psoas) muscles showed weakness before the smaller distal muscles. In others (especially where, as more often was the case, the upper limb failed before the lower) the muscles of the fingers were first attacked, objects fell out of the hand, and digital movements became quickly fatiguing.

The neck and trunk.—Sooner or later, in most cases, the patient became unable to rise, without the help of the arms, from the horizontal to the sitting position. The cervico-cranial muscles often failed at an early date, the head finally falling backwards or forwards and requiring support. Sometimes, before death, the patient was unable to turn in bed.

Urine.—In only one of the undoubted cases was an examination made for toxic substances in the urine, and the result was negative. Senator ([32]) in his alleged case of myasthenia complicating multiple myeloma, found albuminuria and albumosuria. The same condition was also noted by Mendel ([31]) in a non-fatal case which he described. There seemed generally to be no connection between myasthenia and glycosuria, albuminuria, or other abnormal conditions of urine.

Temperature.—In five cases slight pyrexia occurred shortly before death. Otherwise nothing abnormal has been noted in this respect.

Implication of other organs.—Bronchial catarrh, with or without œdema or pneumonia, was frequent towards the close of the disease. Senator's ([32]) suspected case was associated with multiple myeloma; Goldflam's ([22A]) case with a lympho-sarcomatous thoracic tumour; Laqueur's ([30]) case with metastatic deposits of a thymus tumour; Giese's ([28a]), my own, and Schüle's ([15]) with early arterial degeneration; Schüle's with a fatty liver; Strümpell's ([9]), Hoppe's ([12]), and probably Widal and Marinesco's ([16]) with tuberculosis. In two cases a chronic enlargement of the spleen, in two cases an ovarian cyst, and in two cases an

innocent renal tumour were found. Sossedorf's case showed early parenchymatous nephritis, Dreschfeld's ([5]) case granular atrophy of the kidney.

Neuro-muscular lesions.—Of the twenty-two cases on which an autopsy was performed, eight showed no pathological condition of the nervous system. In three cases minute aneurysms or vascular dilatations were noted; and in two the cerebral arteries appeared thickened. Eight cases were examined by Nissl's method, in three (or four) of which was thereby revealed slight chromatolysis. Vacuolation of certain cells of the anterior horns and hypoglossal nucleus with partial degeneration of their nerve fibres was recorded in Mayer's ([18]) case. Hæmorrhages in the central nervous system, always recent and frequently numerous, were found in six cases. The peripheral nerves and muscle fibres were several times examined, in freshly teased and in hardened specimens. In Laqueur's ([30]) and Goldflam's ([22a]) cases the perimysium of several muscles examined contained metastatic deposits of a thoracic tumour. In Sossedorf's case the lingual muscles were degenerated, likewise fibres of the ninth and tenth nerves and their nuclei, but no changes were found in the hypoglossal nerves and their nuclei. This case, however, in my opinion approaches more closely to Eisenlohr's, alluded to on p. 323, than to the cases of true myasthenia gravis.

Course of the disease.—In nearly all of the twenty-two cases improvements and remissions were noted during the progress of the disease. The onset of catamenia, hard work, fear or other emotional excitement, intensified the symptoms and often accelerated the end. Of the above twenty-two cases, death resulted in sixteen from asphyxia; in two from choking; in four probably from exhaustion. We have not sufficient knowledge to give the number of cases that have proved fatal or curable. It is now certain that at least twenty-eight of Campbell and Bramwell's sixty cases ended in death; but the subsequent history of the others is unknown (cf. p. 309).

Duration of the disease.—Of nineteen cases death occurred in eleven between five months and two years after the first onset, in two within four months, in four between two and three years, in one fifteen years, and in another eight and a half years after the initial symptoms.

PART III.

On certain Physiological and Pharmacological Experiments.

In this section the results of such physiological and pharmacological research will be examined as appear likely to elucidate the nature and site of myasthenia gravis. Hitherto I have striven to avoid a natural tendency to locate the most striking character of the disease, *i.e.* the rapid tiring of voluntary movements, in any one part of the neuro-muscular system.

Various conjectures at once arise in the mind when we attempt to account for the premature tiring of voluntary movements in myasthenia. We know that the motor path of the volitional impulse starts in the cortical cells of the Rolandic area. It is conceivable that the tiring is produced by a defective condition in or around the cortical dendritic processes of the upper neuron, in its cell body, or in its descending axis cylinder process.

We know that the axis cylinder process of this upper (or cortico-nuclear) neuron breaks up to surround one or more of the lower (or

nucleo-muscular [1]) neurons of the motor nuclei. It is conceivable that the fatigue is produced by an abnormal condition of the synapse or gap between these physiologically continuous structures. On the condition of such synapses Rabl-Rückhard, Lepine and Duval, Gotch and Lugaro ([33]) have elaborated their several hypotheses of the causes of sleep. There can be no doubt that the cells of the cerebral cortex have considerable influence on those of the motor nuclei. Hemiplegia occasionally causes severe muscular atrophy. The scanning speech of disseminated sclerosis, where the path between the cortical cells and the motor nuclei is alone affected, has been ascribed ([34]) to a preternaturally rapid fatigue of the labial and glossal muscles.[2]

It is also conceivable that the fatigue of myasthenia arises from abnormal conditions in the peripheral nerve fibres, in their intramuscular terminations (end plates), or in the muscular fibres themselves. However, the ordinary fatigue of a healthy man is due rather to central than to peripheral changes. In any prolonged action, the central nervous system becomes tired before the peripheral nervous and muscular systems. The curve of fatigue for volitional action, as shown by Mosso's ergograph, although it varies somewhat according to the subject and his condition, yet differs widely from the curve of fatigue exhibited by a muscle when its nerve is stimulated by numerous rapidly recurring induction shocks.[3]

Nerve fibres themselves seem almost inexhaustible. Both Bowditch ([36]) and Wedenskii ([37]) have shown, the former for warm-blooded, the latter for cold-blooded animals, that nerves may be stimulated for hours by a tetanising current without appreciable diminution of the negative variations in the normal current of rest. By a comparative study of the negative variations in muscle and nerve fibre, Waller ([38]) has proved that the latter tissue is far less readily and more gradually tired than the former.

There is evidence to show that in the exhaustion of a muscle-nerve preparation the end plates are the first structures to be affected. Modifying an experiment of Bernstein, Waller ([38]) made two muscle nerve preparations, the nerves of which he stimulated by two simultaneously applied tetanising currents. In the one preparation the muscle was tetanised to exhaustion; in the other, contractions of

[1] These two words are to my mind preferable to Sherrington's "cortico-spinal" and "spino-muscular," as the cranial motor nuclei are excluded in the latter terminology.

[2] Following the older experiments of Hodge, Guerrini ([35]) has studied the process of fatigue in cortical nerve cells, and finds, according to the degree of exhaustion, increase in the pericellular lymphatic spaces, fragmentation of Nissl's granules, vacuolation of the protoplasm, and marked changes in the nucleus.

[3] The curve obtained by joining the summits of the many contraction waves reaches its highest point at the beginning of the experiment in the case of the muscle contracted by volition, and then descends comparatively quickly to zero; while in the case of the muscle excited by electric stimulation of its nerve, the highest point of the curve is not reached until a greater number of contractions has taken place; and from this point the curve sinks, usually with a far gentler gradient.

the muscle were prevented by the introduction of a constant current passing along its nerve between the muscle and the point of stimulation by the tetanising current. Now it was found that, if the tetanising current were applied directly to the apparently exhausted muscle, it would again enter into tetanus; while, if in the second preparation the constant current were finally broken, the previously resting muscle would at once contract briskly, thus showing that neither the nerve fibres nor the muscle had been in reality exhausted by the tetanising current. By a process of exclusion, Waller inferred that end plates are the first to undergo fatigue.

There are other experiments, which likewise point to the delicate constitution and ready vulnerability of end plates. They seem to be by far the weakest point in the muscle-nerve preparation. Having exposed the sciatic nerve of a recently killed rabbit, Waller ([38]) found that the application of induction shocks to the nerve within half an hour after the death of the animal caused no contraction of the muscles innervated, although the muscles still responded to direct electrical stimulation. Thereupon he cut out the nerve, proved its current of rest by the aid of a galvanometer, and obtained well-marked negative variation by applying to the nerve a tetanising current; that this variation resulted from a purely physiological activity, he assured himself by observing that tetanic excitation of the nerve no longer produced an effect on the variation current, if a tight ligature had been previously passed round the nerve between the point of electric stimulation and the non-polarisable electrodes leading to the galvanometer. Again, Abelous ([39]) severed the sciatic nerve of a frog, and found that when the spinal cord was stimulated long enough to cause muscular exhaustion, the paralysed muscles also became fatigued, but earlier to indirect (nervous) than to direct (muscular) stimulation. Finally, the experiment, by Waller ([38]), of tetanising a muscle alternately by direct and indirect stimulation, when the contractions induced by the latter show far the more evident fatigue, seems to make good the general conclusion that in fatigue of a muscle-nerve preparation the end plate is the first structure to be affected.

It has been supposed that nerve fibres owe their relative inexhaustibility to their protective sheath of Schwann. Mott ([40]) observed that the products of degeneration in peripheral nerves are removed with strikingly greater rapidity than the same products occurring in the central nervous system. In muscle fibres we know that fatigue rapidly ensues if acid phosphates, phosphoric acid, kreatin or lactic acid are allowed to accumulate. Even mental exertion has been shown by Mosso to cause muscular fatigue; and it is well known that the introduction of the blood of a fatigued animal into the circulation of a normal animal will produce in the latter all the cardiac, respiratory, and other signs of exhaustion.

Thus, so far as our physiological knowledge carries us, fatigue in

the individual organism is mainly of central origin, while fatigue in the muscle-nerve preparation is due to the ready vulnerability of the end plates. We pass on to see whether the action of certain drugs on the neuro-muscular system can throw light on the nature of myasthenia gravis.

Veratrine (or physostigmine, digitoxine, or phosphate of soda), when applied to curarised muscle, produces effects strikingly similar to those manifested in Thomsen's disease; where muscles, brought into play during the execution of a voluntary movement, remain contracted for some seconds, although, with successive repetitions of that movement, the contractions approach more and more nearly those of normal muscle.

Now, while veratrine, $C_{32}H_{49}NO_9$, derived from green hellebore, has this curious effect of opposing the relaxation of contracted striated muscle without producing any effect on nerve, a closely allied alkaloid, protoveratrine, $C_{32}H_{51}NO_{11}$, derived from white hellebore, has a totally different action. Between the movements of 'protoveratrinised' animals and the movements of subjects of myasthenia gravis, Jolly ([8]) saw at once a striking likeness. On the ground of Watts Eden's ([41]) researches with protoveratrine, he insisted that its properties supported his contention that in myasthenia gravis the muscle fibres are the structures essentially affected.

However, it is by no means certain that Watts Eden's work can be accepted as final. I gather that he bases his conclusions concerning the direct muscular action of protoveratrine on two experiments. In the first of these he isolates two equally irritable sartorii from the body; and treats one of these with normal saline solution, and the other with saline solution containing protoveratrine. He notices after fifteen minutes a great difference of irritability between the two muscles; and after three-quarters of an hour, the 'protoveratrinised' muscle is markedly fatigued by twenty single induction shocks. An obvious objection to the experiment seems to me to lie in the possibility that stimulation of the small motor fibres and (more especially) the end plates was not excluded. In the second experiment to which I refer, he made two muscle-nerve preparations, the nerve of one of which he dipped into normal saline solution, the nerve of the other being dipped into a solution of protoveratrine. After sixteen hours the nerves showed no difference of excitability.

Since these experiments, others have been conducted by Waller ([43]), which show a distinct effect of protoveratrine on nerves. Indeed, in his writings, Waller concludes that protoveratrine has just that same action on nerve as veratrine has on muscle. Even as veratrine prolongs the katabolic activity of muscle fibre and prevents relaxation from taking place, so, according to Waller, protoveratrine prolongs the katabolic activity of nerve fibre. When a nerve, 'protoveratrinised' *in situ* or after removal from the body, is subjected to a series of

tetanising stimulations, the negative variation produced by each stimulation is never followed by a period of 'restful' positive change. One negative variation follows uninterruptedly on another. There is no break to allow of anabolic reorganisation in the nervous tissue. Instead of remaining constant, as in normal nerve, the negative variations quickly diminish in intensity until, finally, the electric excitability of the nerve is destroyed.

In the face of this result it is difficult to explain the second of Watts Eden's experiments quoted above, so long as we assume that excitability and conductivity of nerve are dependent on the associated electrical changes. I can only suggest that expecting exhaustion, rather than exhaustibility, of nerve, he did not stimulate his nerve for sufficient time to prove his case. But indeed the whole subject of protoveratrine-poisoning requires working out afresh. What seems to be definitely elucidated is its remarkable effect on the metabolism of nerve fibres: whether it has also a direct action on muscle or end plates may be held unproven. That it has a general effect on nerve fibres is also supported by certain of Watts Eden's experiments which go to prove a paralytic effect on sensory nerves.

Lauder Brunton ([42]), Cash, and others have investigated the action of ammonium salts on the muscle-nerve preparation. Lauder Brunton states that "when a muscle has been poisoned by some ammonium salts, a single stimulation applied to the nerve causes a strong contraction like that of an unpoisoned muscle; but a second stimulus has sometimes little or no action, and when the muscle is stimulated directly it soon becomes exhausted." He adds that this paralysing action of ammonium salts, though usually ascribed to their effect on motor nerves, appears to be due to a disturbance of the relation between muscle and nerve,—by which he probably suggests a poisoning of the end plate.

When we attempt to apply what little knowledge we possess of these drugs to the explanation of myasthenic phenomena, we are met at the threshold with several difficulties. We have to remember that it is impossible to argue from electrically produced muscular actions to those volitionally produced. In his case of myasthenia gravis Murri ([21]) showed that the fatigue produced by electric stimulation had no effect on the activity of immediately following volitional contractions, and *vice versâ*; but this was not confirmed by Goldflam ([22a]). Murri found, moreover, that the bodily movements of his patient were completely exhaustible by repeated electric stimulation of the nerves, but were incompletely exhaustible by the will. In the second place, excitability and conductivity of nerve tissue are by no means interdependent properties. It is well known that at the start of regeneration after a nerve lesion a volitional impulse may produce a contraction in the muscles innervated, while the nerve at the point of regeneration is still inexcitable by electric stimuli. These and other difficulties beset us in the application of experimental knowledge to the clinical problems of neurology.

PART IV.

On the Pathology of Myasthenia Gravis.

We come now to consider the various views held by writers on the nature of myasthenia gravis. Wilks ([3]) in his description of the first recognised case of the disease suggested that it arose from a sleep of the lower parts of the central nervous system. Murri ([21]) similarly held that the lesion is "in the neuron which receives the voluntary impulse and transmits it to the muscle." Dreschfeld ([5]) definitely considered his case as one of polio-encephalomyelitis, and did not believe in a toxic origin, which Hoppe ([12]), Goldflam ([22]), Guthrie ([44]), and others have advanced. Jolly ([8]) and Eulenberg ([46]) suggested a dystrophy of the voluntary muscles; Buzzard ([47]), on the other hand, and with him Hoppe ([12]), Senator ([32]), and Goldflam ([51]) were inclined to place the lesion in the higher parts of the brain.

It seems to me in the highest degree improbable that either the muscles or the higher parts of the brain are primarily affected in myasthenia gravis. We know only of one affection appearing (save, perhaps, in the juvenile form of Erb) to be purely muscular in origin, in which definite groups of voluntary muscles are attacked; and that affection, progressive muscular dystrophy, is a congenital one. Comparison between the profound macro- and microscopic changes in this disease and the obscure basis of myasthenia gravis is impossible. Murri and Bramwell, by showing that the movements of myasthenic patients are not improved by massage, have disproved the opinion that the phenomena of unusual exhaustibility are caused by an excessive accumulation of waste products within muscular tissue. Campbell and Bramwell, too, believe they proved that the exhaustion does not lie in the muscle fibres, by their experiment of producing complete myasthenia by faradic stimulation and by volition, after which a galvanic current applied to the muscle gave quite a normal contraction. Here they wrongly supposed that the faradic current must produce its effects by stimulation of nerve, whereas, in point of fact, it will easily produce contraction in muscle fibres devoid of nerves. Even less is there to be said in favour of the view that would attribute myasthenia gravis to a disturbance of the cortical system of neurons. True, we have insisted before on the hold of the upper over the nutrition of the lower neurons. We observe various spastic and flaccid palsies in hysteria where cerebral control may be abnormal, and we have noted a phenomenon similar to the myasthenic reaction in certain cases of cerebral palsy. But as the affections of myasthenia gravis are almost universally bilateral, a series of bilateral cortical lesions would be required: the centre for swallowing, for example, is represented in both cerebral hemispheres. While bilateral cerebral lesions are uncommon, how excessively rare must be a

succesSsion of symmetrical lesions! On the other hand, in poliomyelitis, polio-encephalitis, or polio-encephalomyelitis and in neuritis, bilateral lesions are common enough. A symmetrical invasion is an essential character of the usual forms of a neuritis; and the difficulties in diagnosing certain forms of polio-encephalitis from myasthenia gravis are considerable. So we come to fix our attention finally on the possibly allied diseases of the nucleo-muscular neuron.

The functions of nerve tissue may be impeded by mechanical disturbances in the blood circulation, by the pressure and other effects of new growths, by injury or by inflammation. Inflammation in living matter is almost universally brought about by the action of a poison. The origin of that poison may be from without or from within the body. Within the body it may be produced by disordered processes of metabolism, or may be manufactured by micro-organisms previously introduced. It is now generally recognised that a toxic condition is at the base of most affections of the lower neuron. That such intoxications in peripheral nerves may occur without producing evident signs, post-mortem, is shown in a remarkable way by the following case described by Albu ([48]).

A man, æt. 46, who had had typhoid fever nine years previously but had since enjoyed unfailing health, was seized with sudden general weakness, followed by inability to walk, and pains in the trunk. On the ninth day of his illness he was thoroughly examined, his temperature being 37°·2, his urine free from albumin and sugar. He was found to have flaccid paralysis of both legs. The leg muscles were excessively tender on pressure. His reflexes were normal. He had slight dyspnœa. He could move his arms only with great effort. Two days later all four extremities were completely paralysed. On the thirteenth day of his illness the difficulty in breathing was much greater. On the following day he died of dyspnœa. The brain, spinal cord, peripheral nerves and muscles were examined post-mortem by the naked eye and by the microscope. Sections, prepared with ammonia-carmine, and nigrosine stains and by the Weigert-Pal method, showed no abnormality. The spleen, spinal cord, and blood were proved to be free from bacteria.

Bacteria, however, may cause all the signs of bulbar paralysis without producing corresponding lesions in the nervous or muscular system, as is shown in three cases of typhoid fever described by Eisenlohr ([49]), one of which proved fatal. In all, the reflexes and sensation were normal. The muscles were generally weak. A yellow coccus, indistinguishable from the staphylococcus aureus, was found in the cortex. Neither the cord nor the bulb, examined by Weigert's and Gram's stains, showed any change; the rectus abdominalis and the tongue muscles were degenerated.

That myasthenia gravis results from some autogenetic toxine there can in my mind be little doubt. We know how prone poisons are to cause symmetrical palsies. At one time the presence of a poison, its absence or its impotence at another, will helpfully explain the remarkable variations and intermissions of paresis in this disease. Cases of fatal bulbar peripheral neuritis have been recorded. Bulbar crises in diphtheritic paralysis are well recognised. So that, if it were not for the well-nigh invariable escape of sensory peripheral nerve

fibres, and for the condition of the reflexes and some other important features aforementioned, myasthenia gravis might reasonably be attributed to some such form of toxic neuritis as occurred in the above-described case of Landry's paralysis.

It does not appear to me probable that the implication of sensory along with motor fibres in peripheral neuritis is always the result of the same conditions. No doubt, some cases of peripheral neuritis are due to primary disturbance in the nerve trunks, when the motor and sensory fibres are equally exposed to the action of the toxine carried thither in the blood supply. That sensory neuritis may occur, even to the degree of producing areas of anæsthesia and ataxic signs, is certain; but by far the greater number of sensory disturbances (shooting pains, tenderness, etc.) produced in motor neuritis are to my mind those referable to secondary inflammation of the nerve trunk itself. Recent research into the seat of the primary changes in motor neuritis leads generally to the view that they occur in, or at least near, the motor nerve endings. Now it is well known that chromatolytic changes often occur in the cell bodies of motor fibres affected by neuritis; they have also been observed to follow the disuse (or, it may be, really the lesion) of nerve trunks in cases of amputation. The result of a disturbance at the end plate is to affect the nutrition of the entire neuron, if we can trust the above observations. Hence the whole motor nerve fibre becomes susceptible to the toxine, and the inflammation thus set up in the nerve trunk involves *inter alia* the sensory nerve fibres.

Now a similar sequence of events will well account for the nature of myasthenia gravis. The motor nerve endings are known to be most delicately constituted. If we assume that the poison at an early date affects them, we can understand the changes which Nissl's method of staining has shown in many cases to exist in the motor nuclei. We can also conceive that such chromatolysis may, if the poison be sufficiently active and life continue sufficiently long, lead to a degeneration of motor fibres and to the sensory disturbances which have been met with in a few rare cases of the disease.

But why, alike in neuritis and in myasthenia gravis, should affections of the end plates occur with such remarkable symmetry on both sides of the body? Why should the brunt of the toxic action fall at one time upon the upper, at another upon the lower extremities, or elsewhere? Should we not rather expect such structures as end plates to be affected irregularly and indiscriminately throughout the body? It has often occurred to me that a bilateral vascular disturbance might account for such symmetry of affection; and I notice that Albu, in the above-quoted case of ascending paralysis, suggests that nervous toxines have a primary effect on the vasomotor centres. To explain bilateral nervous lesions we naturally turn to the central nervous system. It is conceivable that through the locally

increased vulnerability of the vessel walls, through impoverished nutrition, or through local disturbances in blood supply, the motor nerve cells in myasthenia gravis become affected before the nerve endings, losing their hold on the end plates with which they are incessantly in touch. Between the nerve cell and its healthy end plate the influence of a constant "tonus" is essential. The nervous impulse, as Sherrington ([50]) observes, is but the "transient glow of an ember continuously black hot." Let us assume, then, that for some reason the cell substance of the neurons loses its power over its axis cylinder processes, and we shall the better understand why the ophthalmoplegia and certain other palsies of myasthenia gravis so closely approximate to the nuclear type,[1] and why bilateral symmetry occurs so regularly in the disease; for we have the same symmetrical character in the chronic paralyses of the bulb and spinal cord.

That the blood vessels of the central nervous system are in some way involved in this disease is perhaps supported by the occasional vascular lesions noticed after death. In two cases thickenings of the cerebral vessel walls were noticed;[2] in three others hyperæmia, vascular dilatation, varicosities, or aneurysms. In every case where hæmorrhages were found, they have been described as recent. In one they were widely distributed, in two they affected the region of the third and tenth nuclei, in another that of the tenth only, in another only that of the sixth. They have always been attributed to changes during the death struggle. But may it not be that the vulnerability of the vessel wall had been exaggerated long before the close of the disease? For the last struggle is invariably a faint one, the condition of the patient being far too myasthenic for him to make markedly convulsive movements.

The final question which now concerns us is the source of the endogenous toxine, or the sources of the toxines, probably various, which may initiate the disease. Several cases in the literature of the disease are suggestive. Senator ([32]) in 1892 published a case of suspected myasthenia gravis which arose during the course of myeloid sarcoma. Albumosuria accompanied it; albumosuria also occurred in Mendel's ([31]) case. More recently Goldflam ([22a]) has published a case of myasthenia gravis, which was associated with a lympho-sarcomatous thoracic tumour and with secondary deposits in the interfascicular tissue of the voluntary muscles. Laquer and Weigert ([30]), also, have recorded a case of myasthenia gravis, where after death a tumour of the thymus gland was found with metastatic deposits in the perimysial

[1] We have, however, to remember, as Goldflam ([22a]) recently has insisted, that the limb muscles are not, as far as we know, attacked in the same peculiar order in myasthenia gravis as in chronic anterior poliomyelitis.

[2] Professor Allbutt points out to me the precociously atheromatous condition of the aorta in two female patients aged 23. Doubtless the toxic condition of myasthenic patients is also indicated by the fatty heart, fatty liver, white kidneys, etc., noted at various necropsies.

tissue of the diaphragm, the deltoid, and elsewhere. These observers refer to a doubtful case of myasthenia gravis, in which a lympho-sarcoma of the thymus gland was found at the necropsy by Hansel-mann. Burr and McCarthy ([51]) note that their case presented an enlarged thymus gland. Goldflam (*loc. cit.*) mentions the case of a man, who, after suffering between 1892 and 1895 from a "very slight benign" form of myasthenia gravis, died in 1901 with all the signs of a mediastinal tumour. Weigert had long ago under his care a patient, concerning whom the diagnosis wavered between cerebral tumour, bulbar paralysis, or perhaps myasthenia gravis, yet in whom post-mortem no signs of bulbar or other disease were found, save a mediastinal tumour similar to that found in Laquer and Weigert's case. Transitory nervous 'hysterical' symptoms are recognised by many neurologists as not uncommon at a very early stage of malignant disease.

It appears probable, therefore, that the development of certain new growths in the body is associated with the formation of a toxine which may give rise to the disease, myasthenia gravis. Bulbar symptoms have been described in more than one case of exophthalmic goitre. Thyroidectomy is one of the conditions which is liable to produce tetany, a disease in many respects the precise opposite of myasthenia gravis, but resembling it in the paucity of lesions found after death. In a few cases of tetany hyperæmia of the pons, bulb and upper cervical region, has been observed; in others vacuolation in the cells of the spinal grey matter; in others rarefaction of intramedul-lary nerve roots. These are just the changes observed in several cases of myasthenia gravis. But while in tetany certain pepto-toxins have been isolated from the urine, in myasthenia gravis no poison has hitherto been detected. The urine, however, has been adequately examined in only one or two myasthenic patients. Obviously further investiga-tion is needed in this direction.

Our knowledge of the physiology of the thymus gland is exceedingly scanty. The gland diminishes so rapidly in size after birth that it is difficult to attach much importance to its functions during post-embryonic life. Abelous and Billard ([45]) find that after removal of both thymus glands in the frog fatal signs of an auto-intoxication set in. They divide these signs into—(α) dynamic, (β) trophic, and (γ) hæmic. Only the dynamic disturbances are produced when one thymus gland is removed; this operation is not necessarily fatal. They find that some antagonism to the effects is produced by a simultaneous injection of calves' thymus extract. The dynamic disturbances consist in—(1) a weak resistance to fatigue, the fatigue curve being shorter and tetanus being less easily sustained; (2) muscular feebleness; and, finally, (3) progressive paresis. Mention is made of experiments by Tarulli and Lo Monaco,[1] who found a perceptible diminution in the force of muscular contractions after

[1] *Cong. internat. de med.*, Rome, 1901.

extirpation of the thymus in dogs. Such observations are suggestive when considered beside the above-mentioned discoveries in certain cases of myasthenia gravis; but at present it is impossible to say more.

PART V.

Summary and Treatment.

Whatever be the source of the toxin, whether or not it arise from interference with internal secretion, it is probable that in the end the nerve endings are mainly affected. Before this stage has been reached, however, the nerve cells of the motor nuclei may for some reason have lost control over the nutrition of the nerve endings. It is likely that the lesions are usually symmetrical, because the bilateral nuclei at any one level of the brain and cord are simultaneously affected by the poison, and thus expose the end plates of each side to its action. From this partial injury a general destruction of the entire neuron may follow, if the disease progress long enough. In many cases, however, no lesion has been found post-mortem; in some a fragmentation and diffuse arrangement of the Nissl granules of the motor nuclei; in one or two rare cases the nerve fibres have begun to degenerate, and muscular atrophy may then conceivably have set in. Usually, however, sufficient vitality still remains in the neuron to keep it and its muscle fibre from actual death; while the metabolic disturbance or exhaustibility of the neuro-muscular system increases and extends, until the embarrassment of respiratory movements finally brings about a fatal issue.

Treatment.—The treatment of this obscure disease can be summed up in two words—complete rest.

Strychnine may perhaps be of use in emergency; but it is doubtful if it has any lasting effect on the course of the disease. Physostigmine, caffeine, cocaine, mercury, potassium iodide, iron, arsenic, spermine, thymus, suprarenal and thyroid extracts, massage, and the electric currents have all been tried in vain. Exposure to cold or to excitement should be rigidly avoided. Fatigue in eating must be carefully guarded against, especially towards the close of the day. Food should be as concentrated as possible, and administered so that the number of movements of deglutition may be reduced to the minimum. In view of the possibly toxic nature of the disease, it is well to attend to intestinal antisepsis. Constipation should above all be avoided; as well to prevent the least trace of copræmia-like poisoning as to avoid the fatigue of passing hard scybalous motions. Menstrual periods seem to be times of great danger. Confinement to bed in a large airy room should be insisted on. When grave signs of bulbar palsy appear, there is but faint hope of recovery. The passage

of the tube of a stomach-pump is attended with great danger, so that only as an extreme measure should the apparatus be resorted to.

PART VI.

Containing the Protocols of Twenty-two Fatal Cases with Autopsy.[1]

Case 1 (described by Wilks) ([3]).—See pp. 309, 310.

Case 2 (described by Oppenheim) ([7], [20]).—P. J., maid-servant, æt. 29, admitted February 21, 1885. Family and personal history satisfactory. For nine months she had complained of weakness of the hands, lately increasing. Objects fell out of her hand. She now had difficulty in going upstairs. Four weeks ago she noticed that she grew tired when speaking and had to pause. She noticed also weakness of the lips, food falling out from her mouth. Difficulty in swallowing next ensued, and all the previous symptoms increased in severity. There had never been pain or other sensory disturbance.

Condition on Admission.—Pupils, discs, and sensory system normal. Face was somewhat expressionless, and moved feebly during conversation. Voice was of moderate power: she could not cry out. Speech was modified by a slight snuffling. The movements of the circumoral and masticatory muscles were very defective; lateral movements of the jaw were impossible. The palate moved feebly during phonation. The tongue could be protruded and moved laterally but feebly; there was slight fibrillar tremor. No atrophy or change in electrical reaction was present in the facial muscles. Pulse was normal. Inspirations were feeble, with deficient expansion of thorax. Patient complained of shortness of breath and of difficulty in coughing. The head moved actively in all directions. Patient had to use her hands when rising from the horizontal position. There was no atrophy in the shoulder, trunk, or upper limbs. There was no muscular rigidity. All the proximal muscles of the upper limbs were equally affected by a remarkable weakness, but without affection of the range or the readiness of their action. Passive movements of limbs were natural. There was some limitation and extraordinary weakness of the movements of the lower limbs. Plantar reflex was only obtained after strong stimulation. Certain muscles (the deltoid and biceps) required a high intensity of the faradic current; otherwise the limbs showed no alternation in electric reaction.

March 1885.—Very little change. The palate still rose in phonation. At times dragging pains in the limbs and face were complained of. *June* 1885.—Nasal regurgitation occurred. Patient frequently complained of short breath, and was at times highly dyspnœic. Evening axillary temperature was 38°·6 C. occasionally. Patient sat propped up. Lungs and other internal organs appeared normal. *July* 1885.—Speech was strongly nasal and very weak. *August* 1885.—Evening temperature for past week had been 39°·2. Patient complained of great weakness and of difficulty in moving the head. Only slight movement of the uvula occurred during phonation. The eyelids and lips could not be tightly shut. The jaw dropped 25 mm. Sensation was normal. Patient could walk but slowly and with small steps. The cough was weak and noiseless. Slight remissions were noticed; but the progress of the symptoms was on the whole continuous. *January* 1886.—Cervical pain was complained

[1] I have excluded from this list Murri's case (described in *Il Policlinico*, vols. ii. and iv. 1895 and 1897), as the necropsy was not performed until six days after death; also Senator's ([32]) case, owing to its complications, and a supposed case described by Raymond in man æt. 70.

of. *May* 1886.—There was no wasting in the muscles of the face or limbs. Patient was much weaker, and had to hold her head up with her hand when in a sitting position. *August* 30, 1886.—She complained of abdominal pain. Temperature, 39°·2 C. An attack of urgent dyspnœa occurred during the night. *August* 31, 1886.—Attacks of dyspnœa. Respirations, 44; pulse, 108; temperature, 38°·2 C. *September* 1, 1886, 3 P.M.—Death.

NECROPSY.—The lungs showed signs of broncho-pneumonia. There was a small fluctuating tumour at the upper pole of the left kidney. The spleen was enlarged and hard. The basal cerebral arteries were thin-walled. The pons, bulb with the cranial nerve roots, the spinal cord, the tongue with the twelfth nerve, the right biceps brachialis muscles with nerves were preserved in Müller's fluid. Serial sections were cut, and stained with carmine, nigrosine, etc. No change was anywhere found save in the region of the seventh cranial nucleus, where an alteration of no pathological significance was noted.

CASE 3 (described by Eisenlohr) ([11]).—The patient, a girl, æt. 18, had from childhood suffered from migraine, sometimes unilateral, at others bilateral, lasting about twenty-four hours, and recurring every two to eight weeks. Occasionally such attacks were accompanied by ptosis. Two years ago (in 1884) she developed diplopia, which she ascribed to a defect in the right eye. After a three months' course of iodide treatment, this disappeared, but returned again a few months later. About the same time ptosis was again noticed, sometimes on one side, sometimes on the other. In July 1886 a severe attack of migraine was followed by weakness of both hands. In the following month there was noticed similar weakness of the legs, shortness of breath on exertion, difficulty in speaking and in swallowing, weakness of the muscles of the neck and jaws. Galvanism and ointments were applied without success. The symptoms constantly varied in intensity.

PRESENT CONDITION.—*August* 16, 1886.—A delicate sallow-skinned girl. She had marked general oculomotor paresis, no diplopia, an external squint in the left eye, partial ptosis more marked on the left side, with inability to raise and close the eyelids completely. The muscles of the face and soft palate reacted feebly. Only small quantities of fluid could be swallowed, and these regurgitated often through the nose. The head was only moved with difficulty. The tongue showed no atrophy, was protruded naturally, with slight fibrillar tremor on the right side. The muscles of respiration were feeble, the cough weak. The electrical reactions of the facial, lingual, palatal, and respiratory muscles were normal. The limbs showed paresis, especially on the left side; the hands were always in a flexed position. No fibrillar tremor nor atrophy was present. Swallowing was difficult at night, although easier in the morning. The knee jerk was present. The reflexes of the upper limbs could not be obtained. Patient was kept in bed, was taking iodides, and was having ointments applied. *August* 17, 1886.—Catamenia. *August* 18, 1886.—An attack of palpitation towards evening. Hurried respiratory movements occurred, with vain attempts to dislodge or swallow accumulated mucus and saliva. Ice-compresses to the face and heart gave relief. A sleepless night. *August* 19, 1886.—Treatment changed to injections of strychnine and application of galvanism. She swallowed and spoke very imperfectly. Tongue was easily tired. *August* 20, 1886.—Breathing was very shallow. Cough was weak. Pulse varied in rate from 108 to 120. *August* 21, 1886.—After a bad night, patient washed herself in the morning. Consciousness was maintained until midday. The diaphragm became paralysed in the morning. Faradic stimulation of the phrenic nerves was vainly tried. Death.

NECROPSY.—The third, fourth, sixth, and seventh cranial nerve-roots were of normal size and colour. The tenth and twelfth were thin but not discoloured; they contained numerous small fibres, which, however, showed no trace whatever of degeneration. The calamus scriptorius and alæ cinereæ were very pale. Treated with carmine and Weigert's stain, the bulb and crura

cerebri appeared normal. At the level of the sixth cranial nucleus there were recent capillary hæmorrhages without change in pigment or alteration in the vessel walls, save great distension of the latter in the neighbourhood. The cortex cerebri and peripheral orbital nerves were not examined.

Case 4 (described by Lauriston E. Shaw) (4).—P. S., æt. 37, a baker, applied for treatment at Victoria Park Hospital on February 11, 1887. Past history satisfactory. A severe attack of diarrhœa, lasting fourteen days, immediately preceded the commencement of his present illness six months ago. This began with ill-defined but increasing general weakness, with occasional remissions, involving the arms, and less markedly the legs and jaws. He was thought to have grown thinner, and had been unable to work since the disease began. Articulation had begun to be difficult, likewise deglutition, especially with liquid food. Within the last fortnight he had had two alarming attacks of dyspnœa.

Present Condition.—He could stand and walk a little unaided, but could not walk long nor go downstairs alone. He could not, when sitting, cross one leg over the other without lifting it with his hands. He spoke slowly and indistinctly, reminding one of a patient suffering from tonsillitis. The mouth was always open, and there was loss of power in the lower facial muscles, causing obliteration of the naso-labial fold. He was unable to whistle or to blow out a light. The loss of power was equal on the two sides. The upper facial muscles were not affected. The tongue was protruded at the start with difficulty, but movements were natural, though slow. The masseters were very weak. Vocal cords moved well; possibly there was some loss of pharyngeal sensation. Diplopia had been noticed by the patient; the pupils, the oculo-motor muscles, and fundi were natural. There was no obvious wasting. His grasp was feeble but equal on the two sides. The wrist and elbow reflexes and knee jerks were brisk,—a little above the average. The cremasteric and plantar reflexes were present. The abdominal and epigastric reflexes were absent. No true clonus was obtained. Memory was normal. Perfect control was retained over bladder and rectum. Heart and lungs were normal. *February* 13, 1887, p.m.—Dyspnœa, probably from intercostal paralysis, was relieved again and again by artificial respiration; no lingual palsy; chest was full of râles. Death.

Necropsy.—No signs of syphilis throughout body. Pons, medulla, and spinal cord were normal to the naked eye. Specimens were hardened in Müller's fluid; and sections were stained, some with aniline blue-black, and some with Weigert's hæmatoxylin stain. Sections were made and examined from the following situations: through the fourth and first cervical segments, at the lowest part of the medulla, through the medulla just before the canal opens, *i.e.* at the level of the eleventh and twelfth nuclei, and from other levels higher up, of which one was through the vagus nucleus and one through the locus cæruleus. The cells of the nuclei, the fibres, vessels and all the tissues in every section appeared normal, and any organic disease of these parts of the nervous system was safely excluded.

Case 5 (described by Jolly and Oppenheim) (8).—Karl K., tanner's apprentice, æt. 15, was admitted August 19, 1890. His family history was satisfactory. The patient had suffered for some years from aural discharge, but felt well when the present illness commenced, carrying heavy weights of skins and working about thirteen hours daily. To his work and partly to self-abuse he attributed his illness. It commenced with weakness in the legs in December 1889. He complained of pain in the sacrum. Soon weakness of the arms and difficulty in rising were noticed, and his speech became a little troublesome. He had suffered occasionally from giddiness and pains in the neck and sacrum. Exhaustion was now so soon produced that after walking a short distance he had to be supported in order to prevent falling; although at the beginning after rest he could walk without support, he rapidly tired and

raised and lowered his pelvis to bring one leg before the other. Similar signs of fatigue ensued when the arms had been exercised. The reflexes were natural, the knee jerks being slightly increased. Sensation, pupils, retinal fundi, and ocular movements were normal. The palpebral fissure was somewhat narrow, but there was no ptosis. After rest, the patient could whistle and blow out a candle; but he soon tired, and no longer could do so. Mastication and deglutition similarly tired; and his speech rapidly became indistinct, though at first quite intelligible. There was no qualitative change in electrical reaction; all the muscles at first responded, some more easily than others, but if one repeatedly stimulated the muscles to produce a tetanic contraction, the contractions became weaker and finally could be evoked only with a very strong current. The patient died March 18, 1891, suddenly while eating. He appeared to die from choking, although the piece of food was immediately removed.

NECROPSY.—Macroscopic examination revealed nothing in the muscles or nervous system. A slight discoloration of the facial and other spinal nerve roots was thought present, but microscopic examination revealed nothing. In fresh teased preparations of muscle, nothing was found. Unfortunately the pieces of muscle preserved for hardening were lost. Sections of the bulb and spinal cord at different level revealed nothing to the microscope.

CASE 6 (described by Hoppe) ([12]). — Hermann H., æt. 40, blacksmith, admitted March 1899. His family history was good; he denied syphilis. For twelve years he had had noises in the ears, but no pain nor discharge. Three weeks ago he began to have difficulty in swallowing, which gradually increased, with loss of taste and inability to masticate his food properly. Soon his speech became nasal, and articulation became impaired. This occurred two days after first his right eyelid had drooped, and then the left. He complained of strongly smelling sweats at night and of bad taste in his mouth in the morning. Sleep was disturbed. Patient was somewhat constipated. Micturition natural.

PRESENT CONDITION.—*May* 26, 1889.—A tall, pale, somewhat thin man. The facial expression was peculiar from the wrinkling of the forehead and the drooping of the eyelids. The right lid was almost completely, the left eyelid partially, closed, so that only the lowest quarter of the left pupil was visible. With exertion the patient could still elevate both lids slightly. The orbital movements were natural. The right eye could be closed more powerfully than the left. There was no asymmetry or loss of movement in the lower facial region; but the angles of the mouth were a little drawn down, giving the patient a somewhat languid expression. The tongue was natural, the pupils were normal. The speech was slightly lisping and strongly nasal. There seemed to be some paresis of the soft palate. He could at present drink fluids without nasal regurgitation, but for every mouthful he made two attempts at swallowing. The outward movement of the vocal cords, especially the left, was impaired; the left cord in phonation had a slightly concave margin. But later laryngoscopic examination discovered paresis of the posterior crico-arytenoids, and no movement in inspiration. The pulse was normal. He was very deaf, and heard a tuning-fork by bone-conduction when he could no longer hear it by air-conduction. Both tympanic membranes were somewhat white and concave. There was no atrophy or loss of power in the limbs. Knee jerks natural. *May* 31, 1889.—He was undergoing iodide and electrical treatment. The right rectus internus and the left rectus superior showed paresis. *June* 1, 1889.—He tired after two bites. *June* 18, 1889.—Patient thought the lower jaw was stronger. Ptosis was slightly better. *June* 28, 1889.—Patient believed he could swallow better. He could no longer whistle. He had marked paresis of soft palate. *September* 12, 1889.—The right ptosis was so far improved that almost the entire pupil was visible. The left eye showed a moderate ptosis. The orbital movements were perfect, save that the

left were somewhat sluggish. The facial nerves showed no alteration in electrical reaction. Patient was discharged. For six months he remained somewhat better; then came gradual progress of the disease. On his second admission, May 8, 1890, speech was markedly nasal and inarticulate. Fluids regurgitated through the nose. Soft palate paralysed. A loud inspiratory stridor occurred occasionally during speaking and at other times. The lips moved naturally and could be closed well, but the patient could not whistle. Lingual movements were natural. Only slight force was necessary to open the patient's jaw while he attempted resistance. Slight left ptosis. *May* 9, 1890.—Complained of weakness in the arms. Emaciation. There was general loss of power in the upper extremities, especially in abducting the shoulder and in extending the elbow. There was no atrophy of the small muscles of the hand. On both sides slight ptosis, especially on the left. Pulse, 104. Fluid did not to-day return through the nose, but swallowing remained as difficult as before. *May* 13, 1890.—Complete inability to masticate. Slight fever. He had to be fed by a tube. Temperature—A.M., 39°·1; P.M., 38°·1. *May* 19, 1890.—Death.

NECROPSY.—Miliary tuberculous pleurisy and peribronchial tuberculous lymphadenitis were found. The cord, bulb, corpora quadrigemina, the basal ganglion, the peripheral nerves and musculature of the tongue and soft palate were treated by the Weigert-Pal method and examined microscopically. No abnormality was found save small fresh hæmorrhages, one in the tenth, two at the level of the third nucleus, and one in the region of the corpora quadrigemina.

CASE 7 (described by Dreschfeld) (5).—Patient was a widow, æt. 36. She had always led a hard life with a lazy, drunken husband. She denied syphilis. Fifteen years ago she suddenly developed bilateral ptosis, which disappeared after six months. A second attack of ptosis, accompanied by diplopia, occurred ten years ago. This was followed by weakness of the jaws and arms, and difficulty in speaking and swallowing. She became unable to whistle and to protrude her tongue. Nine months after this the eye symptoms improved, but the other symptoms persisted. She still continued to work, first as dressmaker, and later in a bakehouse, although she would often have to stop eating because her jaws ached and food would lodge in the mouth between her tongue and cheek. Finally her speech became more and more unintelligible, and difficulty of breathing was noticed.

PRESENT CONDITION.—*November* 19, 1891.—She was a worn, languid woman, with ptosis and almost total external ophthalmoplegia. The intrinsic muscles of the eye were normal. The masseters, pterygoids, and temporals were paretic. All branches of the seventh nerve were affected; she could neither smile nor frown. The tongue lay almost helpless on the floor of the mouth; it was somewhat atrophied. The electrical reactions of the seventh nerve up to the time of death were normal. The palate was paralysed; there was no palatal reflex. Speech was so indistinct that patient replied to most questions by writing. The laryngeal abductor muscles were weak. The sterno-mastoids, trapezii and deltoid muscles were atrophied. There were no fibrillar twitchings in the limbs. The reflexes of the wrist and triceps were markedly exaggerated. Mucus and saliva collected in the fauces and posterior nares; to get rid of the accumulation, patient closed the nostrils with her fingers and made quick respiratory efforts. Pulse was 130. Urine was normal. *November* 22, 1891.—The patient was far worse and weaker, with spasmodic respirations and commencing paralysis of the diaphragm. She was cyanosed and dyspnœic. At night temperature rose to 99°·5, and she died of exhaustion and dyspnœa.

NECROPSY.—There was general bronchitis, commencing atheroma of the aorta, and a dermoid ovarian cyst. To the naked eye, the muscular and nervous system appeared normal. The muscles were not examined microscopically. The whole of the brain, medulla, and cord were carefully hardened for

microscopic examination. Serial sections were made of the pons, medulla, and upper part of the cord, and were stained with various staining reagents, most of them after Weigert's method. No changes, either in the ganglion cells, or in the nerve fibres, or in the neuroglia cells were found. In a few specimens the walls of the blood vessels appeared thickened, and showed slight cellular infiltration in the perivascular spaces, but no hæmorrhages; no degeneration of nerve fibres or atrophy of the ganglion cells could be seen. The nuclei of the cranial nerves showed the ganglion cells in all their integrity, with their processes, and in some places the network of fibres. Some of the cranial and spinal nerves were examined both fresh and hardened, and showed nothing abnormal. Of the motor cortex, and of some parts of the basal ganglion, sections were made and stained, and on examination gave equally negative results as to any pathological changes.

Case 8 (described by Goldflam) ([22], [22a]).—A man-servant, æt. 25, came under treatment on December 22, 1891. His illness began seven weeks previously with cervical numbness, limitation of cranial movements, headache, and giddiness during stooping. A week later the speech and swallowing were affected, then movements of the arms, quickly followed by those of the legs. Latterly he had had tearing pains in the shoulders and sacral region. In the course of two weeks the limbs became so weak that the patient was brought bedridden to an infirmary. Two weeks later (six weeks from the onset) he was sufficiently improved to leave the infirmary. His previous history had been in all respects satisfactory.

Condition on Admission to the Polyclinic.—Patient was a well-developed man, with heart, lungs, and other viscera healthy. His speech was nasal, especially after he had conversed for some time. The soft palate was very slightly movable. The pharyngeal and laryngeal reflexes were markedly diminished. The lower jaw moved feebly. Movements of mastication and deglutition quickly induced fatigue. Bilateral lagophthalmos, diminished conjunctival and corneal reflexes, Graefe's and Stelwag's signs present, weakness of the neck and of all limbs, especially of their more proximal muscles; the head fell forwards. Thyroid gland normal. The knee jerks were active. There were no sensory disturbances, no atrophy, no fibrillar tremors. The electric reactions of the muscles and nerves were normal. Urine was normal. Respiratory movements superficial. Lingual and facial movements normal. Eyes moved and reacted naturally. No exophthalmos. *December* 28, 1891.—Improvement in the limbs, but the movements of deglutition were worse. *January* 9, 1892.—Knee jerks weak and easily fatigued. *January* 16, 1892.—No cervical pain; general improvement. *February* 1, 1892.—A relapse. *February* 8, 1892.—Palatal reflex better. Laryngeal reflex normal. Graefe's sign very slight. Slight double ptosis. *February* 10, 1892.—Palatal and pharyngeal reflexes normal. Fatigue of one limb induced fatigue of the other. *February* 22, 1892.—Variations in the progress of the disease from day to day. *April* 11, 1892.—Continuous improvement. Patellar reflex still feeble. Heel reflex and arm reflexes normal. Patient was discharged, but was unfit for work and tired readily after a long walk. *February* 4, 1893.—Improvement maintained. Treatment had consisted in almost daily transverse galvanisation of the spinal cord, and in the administration of iodine, iron, and arsenic. *December* 7, 1897.—A relapse, in which a new phenomenon developed, namely, a limitation in downward movement of the lower jaw. The legs tired, but not so easily as before. The knee jerks could not be exhausted. There was no myasthenic reaction. *January* 4, 1898.—General advance of the disease. The deltoid and cervical muscles were markedly affected. The patient became dyspnœic when walking. Diminution of excitability of the deltoid and biceps brachii by repeated electrical stimulation. *February* 3, 1898.—Patient had to cease from hard work. *February* 9, 1898.—The left lid drooped more than the right, and its movements were more limited. *July* 15, 1898.—General

improvement. A piece of the left deltoid muscle was excised for microscopical examination [see later]. *November* 25, 1898.—Again a relapse. The myasthenic reaction was not present in all muscles; for instance, it could not be obtained in the triceps brachii. After fatigue of the deltoid and biceps brachii muscles, when they only reacted faintly to the will, faradic stimulation still produced a contraction which was weaker than if there had been no antecedent exhaustion. *May* (end of) 1899.—Dyspnœa, cough, and pricking pains in the right side of the thorax. Patient confined to bed in an infirmary. *July* 13, 1899.—Speech nasal; lips moved feebly. The limbs could now be fatigued to the point of complete paralysis. A large area of dulness and of corresponding weak breathing was found in the chest, beginning in front at the second chondro-sternal articulation, and extending chiefly over the right side. The heart-beat could not be felt. A diastolic murmur was heard in the fourth interspace close to the left sternal margin. Exploratory punctures, with negative results, were made in the right axillary and mammary lines. *July* 19, 1899.—Patient felt better; he had no pain nor cough. *March* 28, 1900.—General condition unchanged. Mediastinal new growth diagnosed. *April* 12, 1900.—At 4 A.M. patient awoke, and having complained to the Sister that he felt unwell, died.

NECROPSY.—The whole of the upper and much of the middle lobe of the right lung was occupied by a lympho-sarcomatous tumour; it was, however, not examined microscopically. The lower lobe and pleuræ contained numerous greyish-red, hard, elastic tumours. The small intestine, and especially the large intestine, contained numerous much enlarged solitary follicles. There was some enlargement of the mesenteric lymphatic glands. Save for considerable hyperæmia of the cerebral pia mater, there was nothing noteworthy in the nervous system to the naked eye. Microscopical examination was confined to the muscles and the nervous system. Nissl's, Marchi's, and Weigert's methods were employed. Neither in the nerves, nor in the cord, nor in the brain was any abnormality found. The piece of the deltoid muscles, excised in July 1898, contained numerous aggregations of small cells, which were likewise found in the muscles removed at the necropsy. The cells resembled lymphoid cells; their nuclei were generally spherical; they lay in the interfascicular connective tissue, surrounding more or less distended blood vessels. Goldflam concludes that these cell collections were metastatic deposits of the lung tumour.

CASE 9 (described by Wernicke and Toby Cohn) ([13]).—A female, æt. 16, maid-servant, was admitted June 16, 1893. Her family history was satisfactory. During a catamenial period in the previous February, she had suddenly developed diplopia, which was followed after a fortnight by left ptosis. This improved, and then came right ptosis. During the next two months patient noticed some stiffness and palsy of the facial muscles; her voice became nasal; she became short of breath after exertion. Then, or perhaps earlier, her arms became weak.

CONDITION ON ADMISSION.—A fairly tall and well-built girl of fair intelligence, with a tendency towards corpulence. Her visual field, optic discs, visual and auditory acuity were normal. She had almost complete bilateral ptosis, and general oculomotor paresis. Facial muscles were almost entirely paralysed. The brow could not be wrinkled. The eyelids could not be shut. The patient could not injure a finger placed in her mouth. Taste and smell were normal. Speech was nasal. Voice was low and hoarse. Slight weakness of the adductor muscles of the vocal cords was noticed. The tongue appeared unusually thin, and could be protruded only very slightly. Sensation was natural. The entire musculature of the upper limbs was paretic and flabby. The hand-grasp was especially feeble; the flabbiness was most marked in the muscles of the scapula, and of the thenar and hypothenar eminences. There was no atrophy. Save hip flexion, all movements of the lower limbs were natural. Knee jerk

brisk ; ankle clonus absent. A certain rigidity occurred in the arms during passive flexion. She could not rise from the horizontal position without using her hands. Possibly a slight quantitative electrical change was present in the reaction of the scapular muscles. The fatigue signs, previously observed by Wernicke in this case, could not be repeated by Toby Cohn. Treatment was begun by nerve tonics, massage, and faradisation. *July* 26, 1893, 9 P.M.—. Sudden attack of dyspnœa occurred, induced by choking while swallowing water. Cyanosis, tracheal rattling. After a quarter of an hour's artificial respiration, patient recovers. General condition was unchanged. *August* 2, 1893.—Meanwhile other fits of choking occurred. To-day a sudden attack of asphyxia came on. Cyanosis, death.

NECROPSY.—All organs appeared healthy to the naked eye. Pieces of the deltoid muscle, brain, spinal cord, and peripheral nerve were hardened in a solution of chromium salts, and were cut and stained with the carmine, nigrosine, hæmatoxylin, eosine, triacid, and Weigert-Pal stains. From single levels of the cord and brain, pieces were hardened in alcohol and treated after Nissl's method, which throughout produced absolutely normal specimens of nerve cells. There was unusual distension of the blood vessels of the nerve roots, more especially perhaps in those of the posterior roots. In the brain this hyperæmia was still more marked. In the internal capsule and cortex cerebri, the vessels seemed more numerous, broader and fuller than usual. Throughout the brain, near these vascular distensions, were numerous recent hæmorrhages of various size. They were especially noted at the level of the central part of the hypoglossal nucleus, and in the entire region of the tenth nucleus ; and were particularly large at the level of the third nucleus. Similar but smaller recent extravasations of blood occurred in the internal capsule, the optic thalamus, and the cortex cerebri. The muscles and peripheral nerves were normal.

CASE 10 (described by Mayer) ([18]).—The patient suffered from difficulty in biting and swallowing, became easily tired, spoke indistinctly, and had bilateral incomplete ptosis. The limbs were paretic, and all symptoms were accentuated towards evening, and were very marked after exertion. The reflexes were normal ; there was no atrophy. Certain symptoms underwent temporary improvement. Death occurred suddenly owing to choking whilst taking food.

NECROPSY.—Six in ninety of the cells of the hypoglossal nucleus were vacuolated, the remaining cells and those of the other cranial and spinal motor nuclei being normal. The intramedullary portions of the anterior roots of the spinal cord and of the hypoglossal roots appeared distinctly atrophied when treated with the medullary sheath stain ; in Marchi preparations these preparations showed numerous streaks of degenerating myelin. It was uncertain how far the axis cylinders participated in the atrophy of the medulla.

CASE 11 (described by Charcot and Marinesco) ([14]).—A boy, æt. 13, without apparent cause, developed total external ophthalmoplegia, total paralysis of the lower limbs, and partial paralysis of the upper limbs, trunk, and face. He died after three months with symptoms of bulbar paralysis. The palsies developed in the order mentioned. The mental and sensory system and the sphincters were undisturbed. The thyroid gland was slightly enlarged ; but this was also the case in the patient's mother. Electrical reaction of the muscles was generally normal, save in certain muscles where an abnormally strong galvanic and faradic current was required.

NECROPSY.—Along the course of the roots of the oculomotor nerve, beside the aqueduct of Sylvius, and at the level of the tenth nucleus, some recent hæmorrhages were found. In all other respects the central nervous system appeared normal ; the peripheral nerves and muscles were also normal.

CASE 12 (described by Strümpell) ([9]).—Marie Z., æt. 21, maid-servant, was admitted in December 1893. Her family and personal history was satisfactory. She had worked hard up to the commencement of her illness in February 1893,

when she first noticed difficulty in speaking and weakness of the eyelids; this she attributed to a chill. Her work in the fields became hard in May; her arms and lips grew tired after use. Almost at the same time the muscles of mastication and deglutition became affected. She could no longer bite or swallow hard food. She several times complained of diplopia and of headache. The symptoms gradually became worse, especially at menstrual periods. At times slight pains in the sacrum and right arm were felt.

Present Condition.—A fairly well-nourished girl. Sensation and intelligence normal. There was a moderate but evident bilateral ptosis, increasing after use of the levator muscles; orbital movements and pupils were natural. The mouth was slightly open and the tongue visible, tending to fall helplessly forward between the teeth. Both lips were somewhat drawn outwards, and their movements restricted. Patient was unable to blow out a candle. The lips could not long be kept closed. There were no fibrillar tremors in the muscles of the lip, face, or tongue. The tongue showed no atrophy, could be protruded fairly well, but could with difficulty be withdrawn or curled tip upwards. The soft palate, covered with mucus, soon lost its power of movement; the muscles of mastication were soon fatigued. General weakness of the limbs was noticed, but without palsy, ataxy, atrophy, or loss of sensation. Skin and tendon reflexes natural. Urine free of albumin or sugar. Pulse varied from 50 to 80. Temperature normal. Rapid exhaustion in muscular power occurred, especially in the tongue, muscles of deglutition, and in the muscles of the limbs. After speaking twenty words continuously, her speech became unintelligible. So also with deglutition and limb movements. If a continuous series of taps were made on the patella tendon, the quadriceps contraction diminished, and perhaps once or several times failed; then with the next tap it recovered itself. Electrical reactions were normal. The myasthenic reaction was not ascertainable, as after forty or fifty strong contractions no fatigue of the radial nerve, or of the muscles governed by it, was observed. It was impossible to fatigue one arm by fatiguing the other. *January* 16, 1894.—Patient fell down helpless, cold, cyanosed, and breathless, with the tongue fallen back. Breathing recommenced after the tongue had been pulled forward by the fingers. A great quantity of saliva and mucus had accumulated in her mouth. The patient sitting upright in bed with the head bent forward. Electric reactions of nerve and muscle were unchanged. Patellar reflex present. Injection of strychnine was given. *January* 17, 1894.—Gradual improvement noticed. *February* 15, 1894.—General condition remained unchanged. Symptoms varied daily. *March* 15, 1894.—Repetition of attacks of dyspnœa. *March* 18, 1894.—Increasing frequency of attacks, during which the limbs were completely powerless. Even at her best she could now only move them slightly in the bed, and with the greatest difficulty. She could no longer raise herself in bed. The cervical muscles were so weak that the head fell forwards or backwards, if unsupported. *March* 20, 1894.—Save for ptosis, ocular muscles were natural. Tendon reflexes feeble, but present. *March* 26, 1894.—A pitiable condition. Patient keeps her mouth open, bending forward to allow the saliva to run out. Frequent attacks of dyspnœa. *March* 27, 1894.—Death from asphyxia.

Necropsy.—No sign of disease was found save miliary tuberculosis of the kidneys. The bulb was stained by Nissl's method, the spinal cord by Pal's method. Neither they nor the nerve roots nor the muscles showed any abnormality under the microscope.

Case 13 (described by Sossedorf).[1]—A governess, æt. 34, was admitted into hospital in June 1895. She had had influenza in November 1893, followed immediately by rheumatic torticollis, and in January 1894 by difficulty and rapid fatigue in speaking. After twelve months she began to masticate and to swallow with difficulty.

[1] Published as an inaugural thesis in Geneva; here abstracted from Oppenheim ([20]), pp. 35, 36.

Present Condition.—Speech nasal. Facial expression sad and motionless. Saliva dribbled during conversation. Labial, lingual, masticatory, and deglutitional movements were very feeble. Sphincter oculi was weak. Slight internal strabismus. No ptosis. No atrophy. No fibrillar tremors. No weakness, exhaustibility, nor ataxia in the limbs. Head moved normally. Occasionally migraine, pains in the arms and back, and paræsthesiæ in the arms. Reflexes and sensibility natural. Pupils normal, occasionally the left was the larger. At the beginning of the illness, diplopia was complained of, but not now. Fatigue easily came on while reading. Muscles of mastication acted well, but were exhausted rapidly. The upper facial muscles were paretic. Electric reactions appeared normal. There was paresis of the soft palate, which was almost immovable, and appeared to react very sluggishly to electric stimulation. Auditory acuity was reduced, buzzing was complained of in the left ear. Pulse and respiration normal. Vocal cords acted normally. The patient's condition varied daily. She was better in the early part of the day. She was treated with injections of strychnine, and later with Brown-Séquard's fluid. Electro-therapeutics and other treatment were also employed. In September 1895 she became much worse; speech almost incomprehensible. No evidence of myasthenic reaction. On January 6, 1896, she died; fatigue, dysphagia, periods of choking and facial palsy having become more and more marked.

Necropsy.—Broncho-pneumonia, pulmonary œdema, general venous congestion, commencing parenchymatous nephritis, and a right renal lipoma were noted. The brain and spinal cord were, with one exception, macro-and microscopically normal. The hypoglossal nerves were normal, but the muscles of the tongue were atrophied and degenerated, and its fatty tissue increased. The hypoglossal nuclei were normal, but the hinder part of the vago-glossopharyngeal nuclei showed slight degeneration, while their roots showed certain changes. The other cranial nuclei were normal.

Case 14 (described by Hall ([10]).—A married woman developed, in November 1896, symptoms of rapid fatigue after exertion, and became generally weak. She could hardly hold up a cup to drink out of. One day she fell down owing to her legs giving way. Two months later bilateral ptosis appeared, more markedly in the left eye. Orbital paresis also developed, varying considerably from time to time, and accentuated towards evening. Under Weir-Mitchell treatment patient improved. After a profuse menstrual period, patient relapsed, developing in addition to the other symptoms a nasal voice, difficulty in swallowing and occasional dyspnœic attacks. Six months after the commencement of the symptoms, patient suddenly "fell ill" while drinking soup, gradually lost consciousness, and died of respiratory failure.

Necropsy.—The brain, pons, and bulb were "examined with great care"; but no pathological changes were discovered.

Case 15 (described by Widal and Marinesco) [referred to in ([16]), more fully described in ([20])].—A man, æt. 31, who had for ten years past suffered from a winter cough and occasionally from hæmoptysis, whose parents died of tuberculosis, developed the following series of symptoms. On December 12, 1896, he had a severe headache. Ten days later, December 21, his right eyelid drooped; on the following day he had bilateral ptosis. On December 24, he was troubled with difficulty in speaking and in moving his tongue. *December* 29, 1896.—Incomplete bilateral ptosis; lagophthalmos; pupils active; convergent squint; no diplopia; patient unable to whistle. Glossoplegia; left naso-labial fold obliterated; paresis of soft palate. Dysphagia and nasal regurgitation; voice weak and hoarse; muscles of mastication weak. The head could not be held erect. The upper limbs were weak, especially the right; the lower limbs were unaffected. Mental and sensory functions normal. The lungs showed signs of phthisis. *January* 1, 1897.—General condition of asthenic palsy. Patient had to support head with hand. He had the facies

Hutchinsonii. Paresis of the abducent nerves, and consequent diplopia. Left facial paresis, and paresis of the right orbicularis palpebrarum. The mouth was half open, saliva dribbling forth. Patient choked when attempting to swallow. The arms were not paralysed, but were very easily tired. He could only stand with support, and was quickly fatigued after walking a few steps. The knee jerks were retained. There was no muscular atrophy. His condition varied from day to day, and was always best in the mornings. The levator palpebræ superioris, the rectus internus oculi, the muscles of the larynx, lips and limbs were easily exhaustible. The patient was very restless, but not delirious. The urine was normal. *January* 2, 1897.—Improvement. *January* 3, 1897.—Dyspnœa and irregular breathing. Pulse small, 120. Patient died suddenly in the night. He had had fever from December 28 onward.

Necropsy.—No mention is made of the naked eye examination, nor of the examination of muscles and nerves. Chromatolytic changes revealed by Nissl's method are found in the cells of the third, sixth, seventh, ninth, twelfth, and accessory nuclei; and corresponding changes in their nerve roots. Marchi's method showed medullary degeneration in the oculomotor, facial, and hypoglossal nerve roots. There were no hæmorrhages, but there was general hyperæmia.

Case 16 (described by Schüle) ([15]).—A woman, æt. 23, was admitted to hospital on August 30, 1897. In the previous February her illness commenced with pains in the limbs. In June she developed a nasal voice, suffered from difficulty in swallowing and regurgitation of fluids through the nostrils. In August she noticed that her legs, and, very shortly afterwards, her arms, were weak. Since June pulmonary catarrh and œdema had made the patient bedridden.

Condition on Admission.—The lungs presented the signs of bronchitis; there was a systolic apex murmur and an accentuated second sound over the pulmonary base. The signs of fatigue were not found in any of the affected muscles. The pupils reacted normally. There was no facial or external ocular palsy. Speech was weak and nasal. Patient had a weak ineffective cough. Swallowing was difficult. There was nasal regurgitation. The limbs moved weakly. The muscles of the neck and trunk were not affected. There was no muscular atrophy or fibrillar twitching. The knee jerk and heel reflex were present, but not brisk. Sensation, mental condition, and sphincters were undisturbed. *September* 4, 1897.—Suddenly severe dyspnœa. Inability to expectorate. Death after three hours.

Necropsy.—The heart was of normal size; there was a small warty deposit on the aortic valves. The liver was fatty. The central nervous system appeared normal to the naked eye, save for numerous grey discolorations of the size of a millet-seed in the region of the olive of the bulb. The methods of Pal, van Gieson, and Marchi were used to stain sections of the central nervous system and peripheral nerves. Nothing abnormal was found save small recent hæmorrhages in the bulb at the level of the tenth nucleus.

Case 17 (described by Oppenheim) ([20]) (pp. 27–33).—A woman, æt. 48, employed in a domestic agency, began to attend Oppenheim's polyclinic on August 20, 1897. She had for six years been suffering from shortness of breath, palpitations, and hand-tremors. For a few weeks in the previous year (1896) she had seen double. She now complained of loss of sleep and appetite, of irregular action of the bowels, of polyuria, and of hyperidrosis. The heart-beats were very rapid. The tremor of the hands was found to be increased in active movements. The tendon reflexes were much increased. No other abnormal condition was noted. The case was diagnosed by Oppenheim's assistant as hysteria (morbus Basedowii?). In October 1897, Oppenheim himself saw the patient. She had then for a month past been complaining of difficulty in speaking and swallowing. He noted that she could not completely and forcibly close the eyelids, and that when the facial

expression was quiet there was slight ptosis. The eyes were otherwise normal. The speech became nasal after protracted talking, and was finally "quite bulbar." She swallowed with difficulty, but without nasal regurgitation. The palate moved well. The pulse varied between 90 and 96. No undue fatigue was manifest after repeated movements of the arms. Electric reactions normal; no sign of myasthenic reaction. The middle and end phalanges of the second and third fingers were not completely extended. Subsequent attempts to elicit the myasthenic reaction failed, save once in the extensors of the fingers, which could rapidly be fatigued by the faradic current. *November* 28, 1898.—Patient complained of great weakness. She could neither whistle nor blow out a light. The soft palate moved feebly during phonation, but showed no obvious signs of fatigue. Diaphragm moved very feebly; respirations slow and shallow. Cardiac action rapid but regular. Knee jerk easily obtained. Fluids could only be slowly swallowed, and made the patient liable to cough. *March* 23, 1899.—Severe attack of dyspnœa, lasting one to two hours. Condition generally worse. Well-marked ptosis, with almost complete palsy of the orbicularis palpebrarum and orbicularis oris. There was paresis of the soft palate, and weakness of the masticatory muscles. The degree of paralysis was variable, but there was no evidence of undue liability to fatigue save in speech, and no myasthenic reaction. The patient was wasted, her skin was yellow-coloured and dotted with pigment spots. Her cough was noiseless. *March* 26, 1899.—Patient was in a state of severe exhaustion and cachexia, dyspnœic, and paralysed as to the muscles of swallowing and the diaphragm. She died on the same (or on the following) day.

Necropsy.—Nothing abnormal was noted by the naked eye. Histological preparations of the brain, cord, nerves, and muscles were made, and stained by the methods of Nissl, Weigert, Van Gieson, Marchi, and others. The sections were examined with great care, and several minute individual departures from the average structure were duly noted. Here and there the perivascular spaces were somewhat wide, and small, quite recent hæmorrhages were met with; but neither could be considered of pathological importance. Neither in the nervous nor in the other tissues of the body was any evidence of disease discovered.

Case 18 (described by Guthrie) ([44]).—A woman, æt. 23, a waitress, was admitted on January 26, 1900, complaining of general weakness and difficulty in speaking and swallowing. Her family history was apparently good; a paternal aunt was epileptic, a sister (later) had a severe attack of chorea gravidarum. The patient had always felt well, and had often worked twelve hours daily during the past four years. She dated the commencement of her present illness from December 1898, when she complained of always feeling tired and of spasm or loss of control over the lower jaw towards the end of the day. In July 1899 this difficulty in speaking increased and became more frequent, while deglutition also was affected, solids and liquids returning through the nose. She also noticed an inability to close her eyes fully. These symptoms gradually increased, and became more marked after exertion or during emotional disturbance. The fingers of the right hand often "dropped."

Condition on Admission.—A slight, pale girl, not markedly anæmic. She had paresis of the orbicularis oris and palpebrarum, of the tongue, soft palate, and probably of the pharynx. She could frown and elevate her eyebrows. There was no ptosis. At times the naso-labial fold was exaggerated owing to elevation of the upper lip. The other muscles of expression were not paretic. She could open her eyes and close them incompletely, but could not make this movement against resistance. There was nothing abnormal in the extrinsic or intrinsic ocular muscles, her vision and optic discs being normal. The mouth appeared weak and was half open. Whistling, formerly possible, could not now be attempted. There were no tremors and no wasting of the face. She could

execute all movements with the tongue save curling it longitudinally; there was no wasting of the tongue, and no tremor until after prolonged protrusion. Speech became rapidly nasal and almost unintelligible after a few minutes talk; it resembled that of persons with cleft palate. Vocal cords acted normally without fatigue. Masseters, pterygoids, and elevators of hyoid appeared normal. The dysphonia and dysphagia varied greatly from day to day, and were always worse at evening or after exertion. Deglutition was rendered difficult through paresis of the orbicularis oris muscle; she appeared also to have lost the normal control of her tongue over the food. Her hand-grasp, recorded by a dynamometer, was, right = 30, left = 40. She gave the same results after four trials. Resistance to passive movements of the elbow, wrist, shoulder, ankle, knee, and hip, though fairly forcible at first, soon became intermittent. Actual weakness was only apparent after emotion. There was no muscular atrophy of the limbs. The tendon and superficial reflexes were normal. The knee jerks could not be fatigued by repeatedly tapping the patellar tendon. The palatal and pharyngeal reflexes could be obtained, but were possibly slightly diminished. There was no ataxy or disturbance of muscular sense nor of sensation. After exertion she complained of fatigue, not of breathlessness. The thoracic and abdominal organs were healthy. The sphincters acted normally. The urine was tested for sugar and albumin, but not for its toxicity. The muscles showed slight diminution to faradism, but no reaction of degeneration. As to myasthenic reactions, the right biceps was completely exhausted in about one minute, the left in one and a half minute, contact being broken from sixty to seventy-five times a minute. The orbicularis muscles of the mouth and eyes were exhausted more easily than the other facial muscles; the least myasthenic muscles were those of the lower extremities. If the faradic current continued to be applied after exhaustion of the muscles, their period of inactivity was lengthened. After three months there was marked improvement. Treatment had consisted in rest and the administration of strychnine. She could now swallow without difficulty, and her speech only became indistinct after several minutes' reading. She felt stronger, and had gained $3\frac{1}{2}$ lbs. in weight. She was discharged in May 1900. *June* 15, 1900.—After some mental worry, her condition had become worse again. *June* 19, 1900.—She could not speak intelligibly or swallow even sips of water. Her mouth was full of glairy mucus and saliva, which she could neither swallow nor spit out. Her neck muscles were so weak that her head fell backwards unless supported by the hands. *July* 2, 1900.—She choked whilst trying to swallow a piece of bread and butter, but her mother succeeded in dislodging it. *July* 10, 1900.—She took to her bed, complaining of great fatigue after a short walk. *July* 11, 1900.—A severe attack of dyspnœa during the night, lasting one hour. *July* 12, 1900.—She was breathing easily and sitting up in bed unassisted. Deglutition was becoming increasingly difficult. Nutrient enemata were given. *July* 14, 1900.—Increasing weakness. *July* 15, 1900.—Paralysis of the diaphragm. *July* 16, 1900.—Death, probably from exhaustion and respiratory failures.

Necropsy.—All the internal organs were healthy, including the brain and spinal cord. The cord, medulla, and portions of cortex, hardened in formalin (5 per cent.), were cut with a freezing microtome and stained with carbol-thionin. The cells of the hypoglossal, glossopharyngeal, and the third cervical nuclei for the most part appeared normal; in some, the chromatophile granules were not differentiated but formed a homogeneous staining, which, however, was not darker than normal. No other changes were detected either in the cells or in the other tissues of the cord. Examination of the cortex and of the nerve trunks gave negative results. The muscles and motor nerve endings were not examined.

Case 19 (described by Myers, Batten and Fletcher, see pages 306, 308).

Case 20 (described by Giese and Schultze) ([28a]).—A married woman, æt. 24,

was admitted on September 2, 1899. Her past and family history was satisfactory. In the early part of May 1899 she suffered from a cough (? influenza), accompanied occasionally by unilateral, usually right-sided, headache. Diplopia appeared, lasting about ten days, and improved by electrical treatment. At the end of the same month difficulties in swallowing and nasal regurgitation developed. A fortnight later came difficulty in speaking, fatigue in the right side of the jaws, and weakness of the tongue. In June 1899, diplopia returned, varying since in degree. In the middle of the month, right ptosis was first noticed, and movements of the thumb and second and third fingers of each hand began to fail, after previous exertion. A burning sensation was felt along the course of the median nerve, but no sensory disturbances have occurred since. The movements of the head and of the arms, especially of the left, became weak. About ten days before admission complete aphonia occurred. General fatigue and sleeplessness is complained of; there has been no fever or giddiness.

PRESENT CONDITION.—A young woman of powerful build, showing no signs of emaciation. She had slight cervical scoliosis. Intelligence and sensation were normal. Her right eye showed slight sub-normal visual acuity. The pupils were equal and reacted naturally. The fundi were natural. Fatigue was shown only after outward and inward movements of the right eye. There was no nystagmus. The right pupil was almost completely covered by the fallen upper lid. There was no left ptosis. The orbicularis muscles of the eye and mouth were paretic. The region supplied by the lower branches of the facial nerves showed no abnormality. The masticatory muscles acted powerfully. There was no difficulty in swallowing. The tongue was protruded straight without tremor. Articulation was good; the voice was aphonic. There was absolute right-sided and almost complete left-sided palatal paralysis. The cervical muscles were natural. The right upper limb was partly paretic. The left ilio-psoas was paretic. Knee flexion on the left side weaker than on the right. The palatal reflex was very feeble, the chin reflex was present. The abdominal reflex was once obtained, arm reflexes were present but weak, the patellar reflex was normal, the heel reflex present, the left being the weaker. There was neither atrophy nor fibrillar tremor. There was no sign of fatigue after use of the muscles innervated by the cranial nerves or of the muscles of the extremities. The vocal cords moved feebly, abduction being particularly weak. The myasthenic reaction was not obtainable. The electrical reactions were qualitatively and quantitatively normal. The edge of the liver was felt below the costal margin. The urine was normal. The pulse was not always quite regular. Treatment was carried out by rest in bed, by administering potassium iodide (and later, iron), also by faradisation. *September* 11, 1899.—The right ptosis had gone; the eyes could be closed better than before. The right naso-labial fold was less marked than the left. There was still no sign of unusual exhaustibility. *September* 12, 1899.—The orbicularis oculi could be fatigued, also the right ilio-psoas. *September* 14, 1899.—Breathing was hurried; the patient used the accessory muscles of inspiration. The diaphragm seemed useless. There were loud tracheal râles, with weak expiratory movement and feeble cough. Volitional exhaustibility was marked in the sterno-cleido-mastoid, left ilio-psoas, and left crural adductors. Swallowing was difficult. The right ptosis had increased. Occasionally there was complete immobility of the palate. The palatal reflex was absent. *September* 17, 1899.—Her general condition was better. The breathing was better and the affected muscles stronger. *October* 3, 1899.—Hitherto no obvious exhaustibility to the faradic current had been observed. To-day the orbicularis oculi when stimulated gave a first contraction, followed by a series of vibratory tremors, but no tetanus was obtained with the strongest stimuli. There was a slight reaction of degeneration in the right levator palpebræ superioris muscle. A.C.C. = K.C.C. in the muscles of the trunk, and in some supplied by the facial nerve. *October* 9,

1899.—Patient could not wrinkle the forehead. The naso-labial folds were bilaterally absent. The muscles of mastication were not exhaustible. Fibrillar tremors readily occurred in the lids and upper lip after prolonged closure of the eyes and mouth. *October* 23, 1899.—Patient was much distressed owing to the death of a child. All her symptoms were much exaggerated. Her pulse was quick; she had marked dyspnœa, and complete paralysis of the musculature of speech, deglutition and mastication. Morphia injections were given. *October* 24, 1899.—Death.

Necropsy.—The skull-cap was very thick; to the naked eye there was nothing abnormal in its contents. Sections were stained in carmine and other stains and by Nissl's method. The microscopic examinations proved of a negative character, save that in some basal arteries there appeared a slight thickening of the intima (arterio-sclerotic change). No hæmorrhages were found. The cells of the third and seventh and other nuclei were normal. Frequently the granules had not the regular arrangement described by Nissl. However, thirty hours had elapsed between the death and the autopsy, and the sections had been hardened in formol and Orth's solution instead of in alcohol. Only the head was examined.

Case 21 (described by Laquer and Weigert) ([30]).—A locksmith's assistant, 30, intelligent and free from syphilitic and alcoholic taint, was seen in August 1900. He complained in the years 1896 and 1897 of attacks of giddiness and palpitations, and in the latter year of attacks of fainting, especially after long walks. He married in 1898. His cardiac condition produced frequent insomnia, but he continued his work. He became fatigued after coitus, and began to complain of pains in the head and body in addition to the previous symptoms. In June 1900 his arms became weak. In July right ptosis occurred. In August slight ptosis of the left eye was also observed, the pupils were unequal, and there was unusually rapid exhaustibility in the muscles of the jaws and throat. His voice quickly became hoarse after reading, and its pitch fell in singing. The right side of the palate seemed narrower than the left. Exhaustion to voluntary movements was easily demonstrated in both deltoid muscles. The muscles affected became increasingly paretic towards evening. One experimental exhaustion of the muscles by voluntary movements appeared to induce temporary cardiac failure; the pulse fell from 72 to 40, was small and feeble, and for five minutes the patient was seriously collapsed. Mind, sensation, nutrition of the muscles and other organs were normal. There was no glycosuria. Patient was confined to bed, and treated with iodides and arsenic. After four months' rest and good food, he returned to light work, having gained 12 lb. in weight and lost in great measure the fatigue of his limbs. After four weeks, however, he could scarcely walk upstairs, and paresis of the muscles of the tongue and deglutition ensued. *January* 16, 1901.—He was bedridden; his cervical and trunk muscles were paretic; he could not raise himself; he had obvious difficulty in swallowing, and spoke with a nasal voice. The left pupil was the larger. The pulse was thin and frequent. Attacks of collapse frequently occurred during the day. The myasthenic reaction was elicited; the muscles were not painful to pressure. At the beginning of February, paresis of the intercostal muscles and diaphragm developed. Expirations were feeble. *February* 6, 1901.—Death, consciousness being retained to the last.

Necropsy.—All organs were normal to the naked eye, save the thymus and the lungs, which finally caused death by aspiration-pneumonia. At the position of the thymus lay a red mass of tissue measuring 5 cms. in length and breadth and 3 cms. in thickness, in intimate connection with the pericardium and the left lung. Sections of this tissue on microscopic examination presented the characteristic features (Hassall's corpuscles, etc.) of the thymus gland. The walls of the smaller veins and some of the arterioles were penetrated by the growing tumour. The pieces of muscles removed,

namely, the deltoid and the diaphragm, appeared normal macroscopically, but their perimysium contained microscopical metastatic deposits, identical with the structure of the thymus tumour, save that Hassall's corpuscles were not found. Similar but more slightly marked collections of cells were found in the cardiac and pericardial tissues. The phrenic and vagus nerves were normal. The central nervous system was examined, but not by Nissl's method. It appeared normal.

Case 22 (described by Burr and McCarthy) ([51]).—A married woman, æt. 19, whose previous history of disease was unimportant (save for mental worry and quarrels with a brutal husband), had a miscarriage, probably induced, in January 1898. A year later she began to suffer from subjective numbness, first in the right hand, later in all limbs and the back. A few weeks before April 1897, when she attended the infirmary, she developed rapidly increasing weakness in the arms and legs. Her condition, when she came first under observation was briefly as follows :—Gait a little stiff. Limbs weak. Patellar and elbow reflexes exaggerated. Slight tremor of the hands and head. The tongue was tremulous, and protruded slightly leftwards. The eyelids trembled and drooped, covering about half of the pupil. They could not be closely apposed nor for long raised. She could not feel a sharp prick on the hands or legs, and only slightly on the face (see later, however). She could, nevertheless, pick up a piece of paper when blindfolded. She could distinguish heat from cold, but felt the distinctions only slightly. She was easily hypnotised.

After being lost sight of for a time, she was admitted into the Philadelphia Hospital on April 23, 1900.

Condition on Admission.—A pale, moderately well-nourished woman of small frame. The head fell slightly forwards, the eyelids drooped, and were in the same state as before. She could lift the head, but only with considerable effort and fatigue. Her limbs moved feebly. There was nowhere distinct palsy (save in the lips and eyes). The speech was slow, weak, and low-voiced. Mastication was slow and wearisome. The knee jerks were large and easily exhausted. The plantar reflex was normal. There were slight but constant choreiform movements in the face and arms. There was no muscular atrophy. Swallowing was difficult, liquids making her cough, and solids seeming to stick in the throat. She still complained of numbness in the limbs, but felt touch, pain, heat, and cold well. Visual acuity of each eye reduced to one half or a third, that of the right being slightly improved by a pinhole. Pupils equal and reacting to light normally. General limitation of orbital movements especially outwards and leftwards. There was a palsy of convergence associated with a variety of ataxic movements. Retinæ healthy, but visual fields concentrically somewhat small. The patient was unable to close her lips. *May* 13, 1900.—No change until to-day, when the difficulty in swallowing suddenly increased, the temperature rose to 101° F., the patient became dyspnœic, with rapid weak pulse, cyanosis, and finally coma. She died the next morning.

Necropsy.—She was pregnant with a three months' fœtus. The left lung had a small calcified tuberculous focus at its apex. The spleen showed chronic enlargement, its capsule was much thickened. The right ovary was cystic. The thymus was enlarged. The brain after being hardened weighed 1250 grms. The pons and bulb were distinctly smaller than usual, the spinal cord was unusually broad in the lumbar region, and, after removal of the dura mater, showed a persistence of the posterior median fissure between the third and fifth lumbar segments. Otherwise macroscopical examination revealed nothing. Sections of the cords, pons, bulb, cortex, and third ventricle floor were stained by the Marchi, Nissl, Weigert, carmine and nuclear stain methods. The cord was normal. There was distinct chromatolytic change, with swelling and displacement of the nuclei, in the cells of the upper nucleus of the vagus nerve. Carmine-stained sections of the vagus nerve showed an

atrophic condition of some nerve fibres. Some swollen axis cylinders were met with in the vagus and hypoglossal nerves. By the Marchi method black dots were found scattered throughout several cranial nerves; but to these no significance could be attached. Microscopical examination of the muscles showed no pathological changes.

REFERENCES.

1. Campbell and Bramwell — *Brain*, London, 1900, vol. xxiii. pp. 277–336.
2. Batten and Fletcher — *St. Barth. Hosp. Rep.*, London, 1900, vol. xxxvi. pp. 213–220.
3. Wilks — *Guy's Hosp. Rep.*, London, 1877, vol. xxii. pp. 54, 55.
4. Shaw — *Brain*, London, 1890, vol. xiii. pp. 96–99.
5. Dreschfeld — *Brit. Med. Journ.*, London, 1893, vol. ii. pp. 176, 177.
6. Erb — *Arch. f. Psychiat.*, Berlin, 1879, Bd. ix. S. 336–350.
7. Oppenheim — *Virchow's Archiv*, 1887, Bd. cviii. S. 522–530.
8. Jolly — *Berl. klin. Wchnschr.*, 1891, Bd. xxviii. S. 660; 1895, Bd. xxxii. S.
9. Strümpell — *Deutsche Ztschr. f. Nervenh.*, Leipzig, 1896, Bd. viii. S. 16–40.
10. Hall — *Brit. Med. Journ.*, London, 1899, vol. ii. p. 1481.
11. Eisenlohr — *Neurol. Centralbl.*, Leipzig, 1887, Bd. vi. S. 337 ff.
12. Hoppe — *Berl. klin. Wchnschr.*, Berlin, 1892, Bd. xxix. S. 332–336.
13. Wernicke — *Deutsche med. Wchnschr.*, Leipzig, 1893, Bd. xix. S. 1184, 1185.
    Toby Cohn — *Ibid.*, 1897, Bd. xxiii. S. 785–789.
14. Charcot and Marinesco — *Compt. rend. Soc. de biol.*, Paris, 1895, Ser. x. tome ii. pp. 131, 132.
15. Schüle — *München. med. Wchnschr.*, 1899, Bd. xlvi. S. 413–415.
16. Widal and Marinesco — (*ref.*) *Neurol. Centralbl.*, Leipzig, 1897, Bd. xvi. S. 509.
17. Kalischer — *Deutsche Ztschr. f. Nervenh.*, Leipzig, 1895, Bd. vi. S. 252–312.
18. Mayer — *Wien. klin. Wchnschr.*, 1894, Bd. vii. S. 166.
19. Déjerine and Thomas — *Rev. neurol.*, Paris, 1901, tome ix. pp. 3–9.
19*a*. Strümpell — *Deutsche Ztschr. f. Nervenh.*, Liepzig, 1898, Bd. xii. S. 115–149.
20. Oppenheim — "Die myasthenische Paralyse," Berlin, 1900, S. 9 *et passim*.
21. Murri — *Arch. ital. de biol.*, Turin, 1896, tome xxv. pp. 64–92.
22. Goldflam — *Deutsche Ztschr. f. Nervenh.*, Leipzig, 1893, Bd. iv. S. 312–352.
22*a*. Goldflam — *Neurol. Centralbl.*, Leipzig, 1902, Bd. xxi. S. 98 ff.
23. Fajersztajn — *Ibid.*, 1896, Bd. xv. S. 833 ff.
24. Allbutt — "System of Medicine," London, 1899, vol. vii. p. 238.
25. Benedikt — "Elektrotherapie," Wien, 1868, S. 51.

26. Brenner	"Untersuch. u. Beobacht. auf . . . d. Elektrotherapie," Leipzig, 1869, Bd. ii. S. 120.
27. Muira	*Mitthl. aus d. med. Fac. d . . . Univ.*, Tokio, 1897, Bd. iii. S. 259–319.
28. Gerlier	*Rev. méd. de la Suisse Rom.*, Genève, 1887, tome vii. pp. 5–29.
28*a*. Giese and Schultze . .	*Deutsche Ztschr. f. Nervenh.*, Leipzig, 1900, Bd. xviii. S. 45–62.
29. Tooth and Turner . .	*Brain*, London, 1891, vol. xiv. pp. 473–495.
30. Laquer and Weigert .	*Neurol. Centralbl.*, Leipzig, 1901, Bd. xx. S. 594–601.
31. Mendel	*Ibid.*, 1901, Bd. xx. S. 111–115.
32. Senator	*Berl. klin. Wchnschr.*, 1899, Bd. xxxvi. S. 161–164.
33. Bradbury	*Brit. Med. Journ.*, London, 1899, vol. i. pp. 1528–1533.
34. Risien Russell	"Allbutt's System of Med.," London, 1899, vol. vii. p. 65.
35. Guerrini	*Lancet*, London, 1899, vol. ii. p. 1087.
36. Bowditch	*Arch. f. Physiol.*, Leipzig, 1890, S. 505–508.
37. Wedenskii	*Centralbl. f. d. med. Wissench.*, Berlin, 1884, Bd. xxii. S. 65–68.
38. Waller	*Brit. Med. Journ.*, London, 1885, vol. ii. pp. 135, 148.
39. Abelous	*Arch. de physiol. norm. et path.*, Paris, 1893, pp. 437–448.
,, ...	*Ibid.*, 1894, pp. 433–439.
40. Mott	*Lancet*, London, 1900, vol. i. p. 1779.
41. Watts Eden	*Arch. f. exper. Path. u. Pharmakol.*, Leipzig, 1891, Bd. xxix. S. 440–472.
42. Brunton	"Text-Book of Pharmacology . . ." London, 1887, 3rd ed., p. 636.
43. Waller	*Brain*, London, 1900, vol. xxiii. pp. 1–38.
44. Guthrie	*Lancet*, London, 1901, vol. i. pp. 393–396.
45. Abelous and Billard .	*Arch. de physiol. norm. et path.*, Paris, 1896, pp. 898–907.
46. Eulenberg	*Deutsche med. Wchnschr.*, Leipzig, 1898, Bd. xxiv. S. 6–8.
47. Buzzard	*Brit. Med. Journ.*, London, 1900, vol. i. pp. 493–496.
48. Albu	*Ztschr. f. klin. Med.*, Berlin, 1893, Bd. xxiii. S. 385–398.
49. Eisenlohr	*Deutsche med. Wchnschr.*, Leipzig, 1893, Bd. xix. S. 122–123.
50. Sherrington	"Allbutt's System of Med.," London, 1899, vol. vi. p. 514.
51. Burr and McCarthy .	*Am. Journ. Med. Sc.*, Philadelphia, 1901, vol. cxxi. pp. 46–52.
52. Gowers	*Brit. Med. Journ.*, London, 1902, vol. i. p. 1253.